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CLINICAL SIGNIFICANCE OF MALIGNANT NEOPLASMS OF THE THYROID GLAND*

WALTER F. ROGERS, JR., M.D.,† SAMUEL P. ASPER, JR., M.D.,‡ AND ROBERT H. WILLIAMS, M.D.§

BOSTON

THE value of extirpating goiters, particularly nodular ones, for the prevention of malignant neoplasms of the thyroid gland has been the subject of considerable discussion for many years. Opinions have ranged from a conservative attitude to one of removing all goiters containing nodules, whether single or multiple.[1, 2] In the presence of these divergent opinions, the frequency with which prophylactic thyroidectomies should be performed needs evaluation.

There are numerous reports in the literature concerning the incidence of malignant neoplasms of the thyroid gland.[3–7] In two recent reports the incidence of carcinoma was particularly high, Cole et al.[7] stating that the incidence was 17.1 per cent in patients with nontoxic nodular goiters, including those with single or multiple nodules, and 7.2 per cent in all nodular goiters, toxic and nontoxic. Such statistics raise an enormous problem if thyroidectomy is to be advocated for all people with nodular goiters, particularly when one considers that in an endemic area the incidence of nodular goiters has been shown to be 80 per cent in autopsy material.[3] Even in nonendemic areas, such as the New England seaboard, Schlesinger and his associates[6] found thyroid nodules, 1 cm. or more in size, which should be clinically palpable, in 8.2 per cent of cases at autopsy. Using the figures of Cole et al.,[7] one might then expect that from 5 to 13 per cent of the people living in an endemic area would suffer from carcinoma of the thyroid gland and that in a nonendemic area the incidence would be from 0.5 to 1.0 per cent.

These hypothetical data show wide discrepancies from actual figures, for in two large series of routine autopsies thyroid carcinoma was found in 1.04 per cent[3] and 1.07 per cent[4] in endemic areas and in 0.095 per cent[3] and 0.109 per cent[4] in nonendemic areas. In 74,335 cases at autopsy in the United States and Europe, tabulated by Wilson,[4] the incidence was 0.26 per cent.

Thus, diagnoses of malignant neoplasms of the thyroid gland appear to be frequent in surgical specimens but rare in clinical and autopsy material. The advisability of removing all nontoxic nodular goiters to eradicate a few potentially cancerous glands should be critically considered along with the mortality and complications resulting from these operations. In addition, the actual effect of so-called "prophylactic surgery" on malignant neoplasms of the thyroid gland should be evaluated.

To help clarify this problem, we reviewed the records of patients with goiter admitted to the Boston City Hospital, the Johns Hopkins Hospital, and the Massachusetts General Hospital in twelve-year (1931–1942), five-year (1940–1944) and eight-year (1937–1944) periods, respectively. The clinical course and pathological lesions in cases of malignant neoplasm of the thyroid gland, diagnosed histologically on autopsy or surgical material, were analyzed. These patients have subsequently been followed for from one and a half to ten years. In addition, the records of 431 patients who had undergone operations¶ for nonmalignant, nontoxic goiter were studied to determine the mortality and complications of this operation.

The large size and location of these general hospitals and the cross section of patients treated should give a good indication of the significance of thyroid cancer in a nonendemic area.

The total number of admissions to the three hospitals in the periods analyzed was 544,918, and goiters were observed in 3221 cases (Table 1). This incidence of goiter, 0.59 per cent, was extremely low and is best explained by the fact that the cases were taken from all the services of large general hospitals and that the neck was not carefully examined in all patients. Table 1 also presents the number of

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Research fellow in medicine, Harvard Medical School; research fellow in medicine, Thorndike Memorial Laboratory, and assistant in medicine, Boston City Hospital.

‡Assistant in medicine, Harvard Medical School; research fellow in medicine, Thorndike Memorial Laboratory, and assistant in medicine, Boston City Hospital.

§Assistant professor of medicine, Harvard Medical School; assistant physician, Thorndike Memorial Laboratory, and junior visiting physician, Boston City Hospital.

¶These operations were performed at the Boston City and Johns Hopkins hospitals.

nodular and diffuse goiters and the incidence of thyrotoxicity.

A pathological diagnosis of malignant neoplasm of the thyroid gland was made in 64 cases, or in 1.99 per cent of all the patients with goiter. Ten additional cases of what appeared to be far-advanced malignant neoplasms of the thyroid gland were not proved histologically; inclusion of these cases makes an incidence of 2.29 per cent in patients with goiter. In the following analysis of cases only those with a histologic diagnosis of a malignant neoplasm are included.

Cancer of the thyroid gland occurred in each of the first eight decades, with constant increments up to the seventh decade, in which 18 of the 64 cases (28.2 per cent) were found (Fig. 1). There were relatively few cases in the eighth decade. Although there was no significant difference between the average ages of the male and female patients, the former being fifty-three and a half and the latter fifty years, there were only 3 males under the age of fifty, whereas 22 females were below that age.

Of the 64 patients, 76 per cent were females, and 24 per cent were males. This ratio of 3:1 is lower than the usual ratio in nonendemic areas, which is estimated to be 6:1 or 7:1.[8]

The patients complained of a variety of symptoms (Table 2). Fifty-five patients, or 86 per cent, with malignant neoplasm of the thyroid gland noted a mass or enlargement of the neck. Further elucidation of the history of the mass, however, was important. In the charts of the 55 patients who had noted a mass in the neck, there was a definite statement in 43 cases regarding whether the patient or a physician had noticed a change in the size of the mass before admission. Thirty-four, or 79 per cent, of the 43 patients had noticed a recent progressive increase in the size of the goiter.

None of the other symptoms was experienced in more than 20 per cent of the patients. Aside from struma, the most frequent symptoms were those of compression of the surrounding structures: hoarseness, dyspnea and dysphagia. Pain in association with metastases to bone occurred in 12.5 per cent of cases. Although a great variety of other complaints were made, these were infrequent and not usually of much aid diagnostically. No patient had symptoms of hypothyroidism.

TABLE 1. *Incidence of Goiters and Malignant Thyroid Neoplasms.*

SOURCE OF DATA	HOSPITAL ADMISSIONS	ALL GOITERS	TOXIC GOITERS			NONTOXIC GOITERS			MALIGNANT THYROID NEOPLASMS
			UNSPECIFIED TYPE	NODULAR TYPE	DIFFUSE TYPE	UNSPECIFIED TYPE	NODULAR TYPE	DIFFUSE TYPE	
Boston City Hospital	406,402	1,125	—	125	306	16	551	127	17
Massachusetts General Hospital	61,117	1,379	—	180	391	—	751	57	10 7* 27
Johns Hopkins Hospital	77,399	717	24	72	210	34	161	216	24 3* 30
Totals	544,918	3,221†	24	377	907	50	1,463	400	74‡

*Not confirmed by histologic examination, but clinical course compatible with diagnosis.
†0.59 per cent of total hospital admissions.
‡0.0136 per cent of total hospital admissions and 2.29 per cent of all goiters.

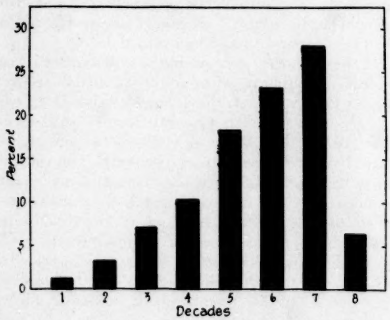

FIGURE 1. *Age of the Patient at the Time of Diagnosis.*

TABLE 2. *Symptoms in 64 Cases of Malignant Neoplasm of the Thyroid Gland.*

SYMPTOM	NUMBER OF PATIENTS	PERCENTAGE
Mass or enlargement of neck	55	86.0
Hoarseness	12	18.7
Dyspnea	12	18.7
Dysphagia	9	14.0
Bone pain (metastatic lesions)	8	12.5
Nervousness	7	10.9
Cough	6	9.4
Weight loss	3	4.7
Palpitation	2	3.1
Paralysis of lower extremities (metastatic lesions)	1	1.55
Hyperorexia	1	1.55
Headache	1	1.55
Irritability	1	1.55
Dizziness and faintness	1	1.55
Chest pain	1	1.55

There was a palpable mass in the neck of 63 patients, or 98 per cent. In 47 cases (73.4 per cent) the masses were nodular in contour, and of these, 37, or 78.7 per cent, had a single nodule; 5 cases were multinodular, and in 5 the exact nature of the mass could not be ascertained. The remaining 17 patients had a diffuse type of struma.

The next most frequent physical sign was enlargement of the cervical and supraclavicular lymph nodes, the former occurring in 23.4 per cent of cases and the latter in 7.8 per cent. Other less common signs were paralyses of the vocal cords, increased areas of retromanubrial dullness, masses in the skeleton and neurologic disturbances. No patient had evidence of hypothyroidism.

In an attempt to analyze the extent of metastases, the course, the mortality and the prognosis of patients with malignant neoplasms of the thyroid gland, it is most important to consider the pathologic classification of these tumors. Lahey, Hare and Warren[9] reported a classification that is extremely useful, the degrees of malignancy being classified as high, moderate and low. The first group included cases of carcinoma simplex, giant-cell carcinoma, epidermoid carcinoma, fibrosarcoma and lymphosarcoma. In our study the patients with a diagnosis of carcinoma (unclassified) have also been placed in this group. The group classed as moderately malignant consisted of papillary adenocarcinoma, alveolar carcinoma and Hürtle-cell adenocarcinoma. The last and least malignant group was made up of adenoma and papillary cystadenoma with blood-vessel invasion.

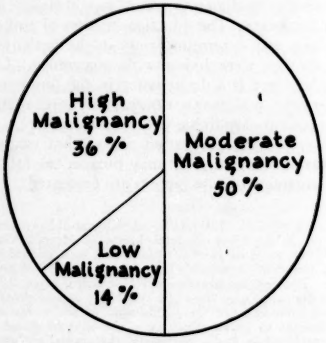

FIGURE 2. *Degrees of Malignancy.*

In this series the proportion of cases falling into the respective groups is shown, and it may be noted that half the 64 cases occurred in the group considered to be moderately malignant (Fig. 2). Thirty-six per cent of cases were classed in the highly malignant group, whereas those designated as low malignancy were relatively infrequent.

Figure 3 presents the extent of involvement in relation to the cervical lymph nodes with subdivision into the respective degrees of malignancy. In 53 per cent of cases the neoplasm was localized to the thyroid gland and cervical lymph nodes, whereas in 36 per cent it had extended beyond this point. In 11 per cent the extent of the lesion could not be exactly evaluated, and the involvement in such cases was classed as "unknown."

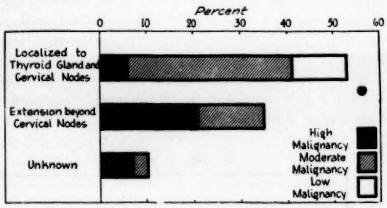

FIGURE 3. *Extent of Spread of Neoplasms.*

It should be noted that the majority of cases with the neoplasms localized to the thyroid gland and cervical lymph nodes were classed as "moderately malignant" (Fig. 3). It is still more striking, however, that all the cases of low malignancy were localized to this region. On the other hand, a relatively small number of the highly malignant lesions were limited to the cervical nodes.

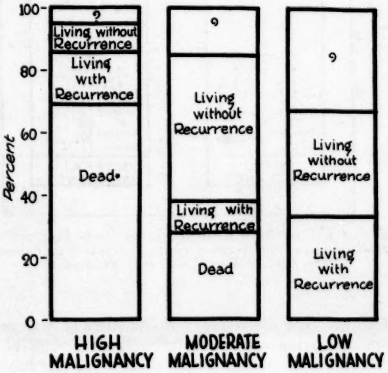

FIGURE 4. *Course of Patients in Relation to the Degree of Malignancy.*

Over half the patients with widespread disease were designated as having highly malignant tumors, and the remainder of cases were classed as moderately malignant. The group classed as unknown were composed mostly of patients with highly malignant tumors. The majority of these patients had large masses in the necks at the time of death, but no permission for autopsy was obtained and the extent of the disease could not be accurately determined.

The mortality was 37.5 per cent, the maximum time of follow-up study being ten and the minimum one and a half years. Of the remaining patients

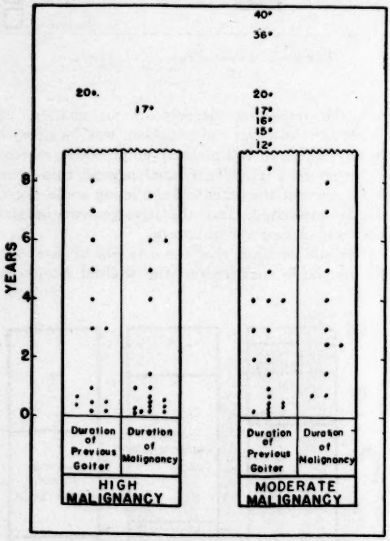

FIGURE 5. *Duration of the Goiter previous to the Diagnosis of Malignancy and the Duration of the Malignancy in Patients Who Died or Were Living with Recurrence.*

15.5 per cent are living with recurrence, 31.2 per cent are living without recurrence, the fate of 12.5 per cent is unknown, and 3.3 per cent died of intercurrent disease. More revealing, however, is the course of the patients in relation to the degree of malignancy (Fig. 4). It is seen that 69 per cent of patients with highly malignant tumors are dead and that 17.4 per cent of the others had a recurrence of the disease. In the moderately malignant group, the largest share are living without recurrence, whereas 38 per cent are dead or living with recurrence. Among those with tumors of a low degree of malignancy, there were no deaths, but the number living with and without recurrence was equal. As the degree of malignancy declined, less was known about the fate of the patients, probably owing to the fewer symptoms in the patients with more benign lesions, who failed to return for follow-up study.

The duration of goiters before the diagnosis of cancer and the duration of the lesions after diagnosis in patients with highly and moderately malignant tumors is shown in Figure 5. Some patients with highly malignant neoplasms had long-standing goiters, but a large number had goiters of less than one year's duration. In the patients with moderately malignant lesions the goiters were of longer duration, and 15 patients, or 55.5 per cent, had goiters ranging from three to forty years. Likewise, the duration of the disease after the diagnosis had been established was usually less than two years in the highly malignant cases, whereas that in the moderately malignant cases was usually longer than two years. The duration in cases of malignant neoplasm was determined only in the patients who had died or were living with recurrence. Consequently, there is a discrepancy in the number with moderately malignant tumors, because many of these patients are living without recurrence.

To emphasize the varied course that malignant neoplasms of the thyroid may pursue, the following brief abstracts of case reports are presented.

CASE 1 (B.C.H. 1,011,410). A 52-year-old woman was admitted to the Massachusetts Memorial Hospitals in January, 1941, with the chief complaint of a mass over the right eye of 5 months' duration. There was no history of previous goiter. Physical examination revealed a firm mass, 2.5 by 1 cm. in diameter, over the right eye, and a nodule protruding upward from beneath the manubrium of the sternum that was thought to be an adenoma of the thyroid gland. The substernal nodule and a portion of the cranial nodule were removed. The histologic diagnosis of the former was small-cell carcinoma arising from an embryonal adenoma, and the mass in the cranium was reported as metastatic carcinoma of the thyroid gland. The patient was then transferred to the Boston City Hospital, where the skull lesion was resected. After operation, she made an uneventful recovery and was well for 5 years, when there was evidence of recurrence of the tumor in the skull. X-ray therapy effected some regression of the lesion. Otherwise, the patient has remained in good health.

CASE 2 (M.G.H. 161,672). In 1928 a 53-year-old woman was admitted to the hospital complaining of a mass at the medial end of the left clavicle. This was removed and was diagnosed as a carcinoma arising in the thyroid gland. After the excision, the patient did well for 11 years, when she began to complain of hoarseness and swelling of the neck, accompanied by pain in the right clavicle and chest. Physical examination at that time revealed a pulsating tumor mass, the size of a hen's egg, at the medial end of the right clavicle. In addition, there were some small nodules surrounding the mass. A biopsy specimen, obtained by needle, was diagnosed as a rapidly growing fetal adenoma, and an x-ray film of the chest was consistent with metastatic cancer. The patient was given x-ray therapy to the right side of the neck and upper mediastinum, with a decrease in the size of the masses in both areas. General improvement followed, and for the next 5 years the patient remained well except for slow growth of the mass in the right side of the neck. At the end of that period she also had pain in the right arm and a destructive lesion in the ilium. She received x-ray therapy to the

mass in the neck and to the lesion in the ilium without any noticeable clinical improvement. Five months later she died at home, 17 years after the initial diagnosis of carcinoma had been made.

These cases illustrate the long course that carcinoma of the thyroid gland may take, despite the presence of widespread metastatic lesions.

On the other hand, some patients pursued a rapidly fatal course, as in the following case.

CASE 3 (M.G.H. 466,945). A 58-year-old man entered the hospital complaining of hoarseness and headaches of 3 months' duration, accompanied by weight loss. There was no history of goiter. Physical examination showed a swelling of the right side of the neck, with a hard irregular mass involving the thyroid gland and extending superiorly and attached to the deep structures. In the hospital he rapidly became worse and shortly after admission contracted an upper respiratory infection, followed by pneumonia and death. Autopsy revealed a small-cell carcinoma of the thyroid, with metastatic lesions in the brain, kidneys, adrenal glands and cervical lymph nodes. The entire course of the illness was less than 4 months.

The correct diagnosis was made clinically, or was suspected, in 31 (48 per cent) cases in this series. As would be expected, the correct diagnosis was made more frequently in patients with highly malignant tumors. In the cases in which a correct clinical diagnosis was made 48.5 per cent of patients are dead, whereas in those in which the diagnosis was benign lesions of the thyroid gland, 24 per cent are dead.

Thyroid cancer accompanying thyrotoxicosis is considered rare. In 168 cases of thyroid cancer Ward[1] found 1 case of carcinoma in "a diffuse toxic goiter." Crile[10] observed 1 case of hyperthyroidism in 249 cases of malignant thyroid neoplasm, and Means[8] stated that thyrotoxicosis might almost be considered insurance against cancer of the thyroid gland.

Five (7.8 per cent) of the 64 patients with malignant thyroid neoplasms had thyrotoxicosis. These cases occurred among 1308 patients admitted with hyperthyroidism during the respective time intervals reviewed, making an incidence of malignant neoplasms of the thyroid gland among thyrotoxic patients of 0.38 per cent. In none of the 5 cases was cancer suspected, and all patients had thyrotoxicosis at the time of operation. All the patients were in the sixth and seventh decades, however, and all were women. The degree of thyrotoxicosis was variable, since 3 cases were considered moderate, 1 severe and 1 mild. Two patients had diffusely enlarged glands without nodules, 2 had diffusely enlarged glands with single nodules, and the remaining case had nodular enlargement of the thyroid gland. The pathological picture in these cases was varied, since 3 were diagnosed as carcinoma (unclassified), 1 as giant-cell carcinoma and 1 as cystadenocarcinoma. The patient with cystadenocarcinoma is living without evidence of recurrence, whereas the patient with the giant-cell carcinoma had a recurrence of the disease, although at present she is in fairly good health. Of the 3 patients with unclassified carcinoma 1 died with extensive metastases, and the remainder are apparently well despite the fact that the surgical specimens showed invasion of the veins with tumor in 1 case and the presence of a metastatic lesion in a cervical lymph node in the other.

Since thyroidectomy is frequently advocated for "prophylaxis" against cancer, it is of particular interest to determine the effectiveness of this principle in patients in whom there was no clinical suspicion of cancer before operation.

These patients may be divided into two groups: those who, so far as could be ascertained, had no evidence of neoplastic disease at the time of initial operation and who later developed cancer, and those who were not suspected of having malignant lesions until the specimens had been examined by the pathologist.

The first group is composed of 7 patients who had similar clinical courses in that they had had operations for a goiter at some previous date. This operation was followed by a recurrence of the mass, which at a second operation proved to be the site of a malignant process. In 5 patients the neoplastic disease was found twelve, thirteen, sixteen, twenty-four and thirty-four years after the initial operation. Adenocarcinoma was noted in 3 patients, and papillary adenocarcinoma in the other 2. Two patients died of intercurrent disease, 2 are living without recurrence, and 1 is living with a recurrence of the disease. It might be said that these were cases of low-grade malignancy and that the initial operation had been inadequate or that the surgical specimen was not examined carefully enough. This is granted, since in some cases there was no way to determine how thoroughly the initial specimen had been examined. This does not negate the fact, however, that these patients had carcinoma despite prophylactic surgery, and there is reasonably

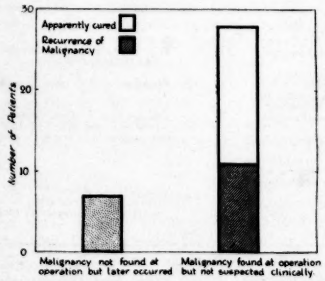

FIGURE 6. *Patients in Whom a Malignant Neoplasm Was Not Suspected but on Whom a Thyroidectomy Was Performed.*

good evidence that malignant lesions had not been present at the initial operations.

An illustrative case is the following:

CASE 4 (B.C.H. 906,993). A 62-year-old woman entered the hospital because of recurrent masses in the neck. Twelve years previously she had had a resection of an adenoma at the Lahey Clinic, the specimen having been diagnosed as papillary cystadenoma. Twelve and 14 years, respectively, after operation she entered the Boston City Hospital for recurrent masses in the neck, ranging from the size of a pea to that of a golf ball. These nodules were removed and each time were found to be papillary adenocarcinoma. On the last hospital admission, 16 years after the initial operation, she was admitted for bloody stools, and a diagnosis of carcinoma of the rectum was made. She still had a nodule in the neck, 4 cm. in diameter. An abdominal laparotomy and resection of the rectum were advised, but the patient refused operation. She later died at home, apparently from carcinoma of the rectum.

Of the remaining patients in this group, 1 underwent the extirpation of a thyroglossal-duct cyst, and ten months later a mass recurred, was assumed to be a recurrent thyroglossal duct cyst and at operation was found to be a papillary adenocarcinoma of the thyroid gland; the other patient was operated on for an adenocarcinoma of the thyroid gland nine months after the removal of a fetal adenoma. It seems probable that at the time of the first operation each of these patients harbored a malignant neoplasm that was overlooked.

The second group is composed of the 28 patients who were not suspected of having malignant neoplasms until after histologic examinations of thyroid tissue had been made (Fig. 6). Among these there were 11 who had a recurrence of the tumor, with 6 subsequent deaths.

TABLE 3. *Complications of Operations in 431 Cases of Nontoxic Goiter.*

COMPLICATION	NO. OF CASES	COMMENT
Vocal-cord paralysis	13	Four patients had large glands, and 1 had Hashimoto's disease
Wound infection	11	—
Hoarseness	10	Duration of 3 days to 2 months
Marked swelling of neck, with fever	9	—
Hypoparathyroidism	7	Transient in 5 cases; duration of 1 year or longer in 2.
Hypothyroidism	5	One patient had chronic thyroiditis
Hematoma	3	—
Postoperative hysteria or delirium, or both	3	—
Massive hemorrhage	2	—
Dysphagia	2	Transient but severe
Anesthetic accident	1	Cardiac arrest; restoration of cardiac function with intracardiac adrenalin.
Total	66 (15.3%)	

The two groups of cases discussed above lend support to the statement of Hertz[11] that after multiple operations on thyroid glands, cancer has developed despite the "prophylactic surgery."

To evaluate the principle of the extirpation of goiters, the complications resulting from such a procedure were determined by a review of the charts of 431 patients who had had a thyroidectomy for nontoxic goiters, diffuse or nodular. It was borne in mind that the complications in these cases were probably more frequent than those in a series of cases in which all goiters were routinely removed.

There were 5 fatal cases, or a mortality of 1.16 per cent. The majority of these cases, however, had features that greatly increased the hazard of operation. Thus, 2 patients had dyspnea, dysphagia and pressure symptoms, caused in 1 case by a Riedel's struma and in the other by a large adenoma (10 x 10 x 15 cm.) with abscess formation. The glands were removed with great difficulty in both cases. The first patient died on the fourth postoperative day, with an autopsy diagnosis of bronchopneumonia and damage to the recurrent laryngeal nerves, and the second died on the first postoperative day with a clinical diagnosis of pulmonary embolism. A third patient was found to have substernal extension from a nodular goiter and died on the first postoperative day, having become flushed, toxic and delirious. The clinical impression was that the patient died of pneumonia, but autopsy was not performed.

A seventy-three-year-old woman with a 7.5-cm. nodule in the right lobe died on the third postoperative day of pneumonia and cardiac failure. Another female patient, aged sixty-one years, had a nodular goiter removed without great difficulty, but it was noted at operation that the trachea was the size of the surgeon's fifth finger. Postoperatively, the patient had respiratory distress and difficulty in speaking, and she died during the second postoperative day.

The various complications of operations on patients with nontoxic goiter are presented in Table 3; of these patients, 15.3 per cent suffered from one or more operative complications, the most significant of which consisted of 13 cases of vocal-cord paralysis, 7 of hypoparathyroidism and 5 of hypothyroidism. Complications such as massive hemorrhage, hematomas and anesthetic accidents, of course, did not involve long-term disability, but at the time caused a definite threat to life.

DISCUSSION

It is admittedly difficult to determine when a goiter contains a malignant neoplasm, particularly a neoplasm that arises in a previously existing adenoma or one of low malignancy. Because of this problem, it has been suggested that every nodular goiter should be "prophylactically" removed.[1, 2] This type of reasoning is not regarded as justified, particularly in the light of the figures presented above. Some selection of cases is considered possible, and prophylactic surgery is not reducing deaths from malignant neoplasms of the thyroid gland as much as has been implied.

We have found the clinical incidence of malignant neoplasms of the thyroid gland to be low — much lower in fact than one would expect from previously cited figures on surgical specimens.[3, 7]

In this report, particular stress has been placed on the pathological lesion and its degree of malignancy because the clinical course of the patient depends so much on this factor. The majority of patients who died of malignant neoplasms of the thyroid gland or had widespread extension had tumors that were classed as highly malignant. These highly malignant tumors, as emphasized by Clute and Warren,[12] were usually characterized by a sudden appearance of a mass in the neck, although at times they arose in a previous goiter, and pursued a rapidly fatal course. Such tumors are rarely removed completely by prophylactic surgery.

On the other hand, in the cases classed as tumors of moderate or low malignancy there were few deaths (none in the latter), and the results of treatment were fairly satisfactory. Even when clinically suggestive of malignancy, these tumors are often amenable to treatment. This point of view is likewise held by Pemberton.[13] These tumors, then, with a better prognosis, are frequently said to be "cured" by prophylactic surgery. When one considers, however, that even when a benign tumor of the thyroid gland or a clinically unsuspected malignant neoplasm is removed, development or recurrence of a malignant neoplasm is not infrequent, the value of routine prophylactic surgery on all nodular thyroid glands becomes less impressive.

As in other reported series, the patients in whom a correct diagnosis was made had the highest mortality rate. This does not necessarily mean that prophylactic surgery would have obviated this, because as pointed out above, the majority of these patients had highly malignant types of tumors in which the onset and course of the disease was of short duration, despite various types of therapy.

The incidence of operative complications in cases of nontoxic goiters should also be considered. If the 431 cases in this report are considered to be an average illustrative example, it is seen that many operative complications and even death may occur. Although it is said that extirpation of nontoxic goiters and adenomas should be without risk, this seems to be a goal more sought after than actually obtained, particularly when applied to all clinics and hospitals.

Single nodules or masses in the thyroid gland are the most frequent site of malignant lesions. This has been particularly emphasized by Lahey.[14] The greatest number of patients studied likewise had a single nodule or mass as the site of the neoplasm. Thus, it seems that many of these single nodules should be removed, particularly in young people, for in a nonendemic area nodules are rare below the age of thirty,[6] and should arouse suspicion of a malignant lesion. On the contrary, it seems unnecessary to remove all multinodular glands because they are infrequently the site of cancer and so prevalent, even in nonendemic areas, that the disadvantages of removal outweigh the advantages. Some pathologists have considered nodules in the thyroid gland to be "almost physiological," especially in women after the age of fifty.[6]

Certain signs in a gland with one or more nodules, however, are indications for removal of the nodule. They are any increase in size, especially in the absence of thyrotoxicosis, and any suggestion of increased firmness or fixation of the surrounding tissue. The first sign is probably the more important because the other connotes more extensive involvement. Multinodular goiters may well be treated conservatively but deserve careful observation.

Of the patients with malignant neoplasms of the thyroid gland 7.8 per cent had thyrotoxicosis. This figure is slightly higher than that in other reported series.[1, 6, 13] It is still to be noted, however, that cases of malignant neoplasm accompanying thyrotoxicosis are rare, for in 1308 cases of thyrotoxicosis there were 5 patients (0.38 per cent) with malignant neoplasms.

What effect the treatment of thyrotoxicosis with thiouracil will have on thyroid cancer must await future evaluation. Bielschowsky[15] has shown that simultaneous administration of 2-acetyl-amino-fluorine and allyl-thiourea produced adenomas and malignant neoplasms in the thyroid glands of rats, whereas either of these drugs used alone did not produce the neoplastic lesions. We have administered 2-acetyl-amino-fluorene and thiouracil simultaneously to a series of 12 rats, and although malignant tumors of the breast and other organs developed in 8, the only detectable lesion in the glands was hyperplasia. To date, there is no clinical evidence that thiouracil is a predisposing factor or that it has increased the incidence of cancer.

Regarding "prophylactic surgery" for nodular or diffuse goiter in the prevention of thyrotoxicosis, we believe that this complication can be well treated, should it arise, with antithyroid drugs and surgery.

Summary

The total number of patients admitted to the Boston City Hospital, the Johns Hopkins Hospital and the Massachusetts General Hospital in periods of twelve, five and eight years, respectively, was 544,918. Among these patients there were 3221 with goiters and 64 with a histologic diagnosis of a malignant neoplasm of the thyroid gland.

The clinical picture and the course of the patients with malignant thyroid neoplasms are discussed, with particular reference to the types of pathological lesions and their degree of malignancy.

It was found that in clinical and autopsy material malignant neoplasms of the thyroid gland were infrequent. The majority of patients dying of malignant lesions had highly malignant tumors that were generally of rapid onset and of short

duration, and in these patients "prophylactic" surgery had rarely been performed.

Patients with thyroid tumors of lesser degrees of malignancy do not have a hopeless prognosis. Sometimes, even with apparently widespread metastases, they live for more than ten years.

It is not believed that all nodular goiters should be removed. Despite "prophylactic" surgery on benign or clinically unsuspected malignant goiters, lesions may later develop or frequently recur. Moreover, operations on patients with nontoxic goiter are associated with a significant number of complications and are sometimes fatal.

Single nodules, particularly in young people, should in most cases be removed, and any nodule showing an increase in size, in the absence of thyrotoxicosis, or in firmness or fixation should be extirpated.

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References

1. Ward, R. Malignant goiter. *Surgery* **16**:783-803, 1944.
2. Hinton, J. W., and Lord, J. W., Jr. Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? *J. A. M. A.* **129**:605, 1945.
3. Wegelin, C. Schilddrüse. In *Handbuch der speziellen pathologischen Anatomie und Histologie.* Edited by F. Henke and O. Lubarsch. Vol. 8. *Drüsen mit innerer Sekretion.* 1147 pp. Berlin: Julius Springer, 1926. Pp. 1-547.
4. Wilson, D. B. Malignant tumors of thyroid. *Ann. Surg.* **74**:129-184, 1921.
5. Coller, F. A. Adenoma and cancer of thyroid: study of their relation in ninety epithelial neoplasms of thyroid. *J. A. M. A.* **92**:457-463, 1929.
6. Schlesinger, M. J., Gargill, G. L., and Saxe, I. H. Studies in nodular goiter. I. Incidence of thyroid nodules in routine necropsies in nongoitrous region. *J. A. M. A.* **110**:1638-1641, 1938.
7. Cole, W. H., Slaughter, D. P., and Rossiter, L. J. Potential dangers of nontoxic nodular goiter. *J. A. M. A.* **127**:883-888, 1945.
8. Means, J. H. *The Thyroid and Its Diseases.* 602 pp. Philadelphia: J. B. Lippincott Co., 1937. P. 482.
9. Lahey, F. H., Hare, H. F., and Warren, S. Carcinoma of thyroid. *Ann. Surg.* **112**:977-1005, 1940.
10. Crile, G., Jr. Hyperthyroidism associated with malignant tumors of the thyroid gland. *Surg., Gynec. & Obst.* **62**:995-999, 1936.
11. Hertz, S. Discussion of Lahey.[14]
12. Clute, H. M., and Warren, S. Prognosis of thyroid cancer. *Surg., Gynec. & Obst.* **60**:861-874, 1935.
13. Pemberton, J. de J. Malignant lesions of thyroid gland: review of 774 cases. *Surg., Gynec. & Obst.* **69**:417-430, 1939.
14. Lahey, F. H. Carcinoma of thyroid. *Am. J. Roentgenol.* **46**:469-475, 1941.
15. Bielschowsky, F. Tumours of thyroid produced by 2-acetyl-aminofluorene and allyl-thiourea. *Brit. J. Exper. Path.* **25**:90-95, 1944.

USE OF PENICILLIN IN THE TREATMENT OF CARRIERS OF BETA-HEMOLYTIC STREPTOCOCCI AMONG PATIENTS WITH RHEUMATIC FEVER

Jessamine R. Goerner, M.D.,* Benedict F. Massell, M.D.,† and T. Duckett Jones, M.D.‡
With the Technical Assistance of Mary Meyeserian

BOSTON

THE danger of hemolytic streptococcus respiratory infection to persons who are susceptible to rheumatic fever is well recognized. Since with present knowledge there are inherent difficulties in evaluating the innocuousness of a given strain, every carrier of beta-hemolytic streptococci must be considered a potential menace to a population of rheumatic-fever patients. Prolonged isolation of such carriers is inadvisable from the psychologic standpoint and is usually impracticable. Hence, means of abolishing the carrier state are desirable.

During the administration of sulfonamides to carriers the throat cultures become negative for hemolytic streptococci in some cases, whereas in others the cultures, although remaining positive, usually yield only small numbers of the organism. In most cases, however, when therapy has been discontinued, nose or throat cultures again become strongly positive.[1–11]

Many investigators have found penicillin to be a more effective agent than sulfonamides for the treatment of hemolytic streptococcus respiratory infections. From these reports it also seems that during penicillin therapy hemolytic streptococci disappear from the nose and throat in nearly all cases. After the discontinuation of treatment the organisms have reappeared in a varying proportion of the reported cases, depending apparently on the dose of penicillin and the number of days of treatment.[7–18]

With a view to preventing the spread of hemolytic streptococci from one patient to another, since November, 1945, penicillin has been administered to all patients at the House of the Good Samaritan found to have positive throat cultures. The following brief extracts of cases observed at the hospital in the early autumn of 1945 illustrate the need for the elimination of beta-hemolytic streptococci from the upper respiratory tract of carriers.

Case 1. W. J., a 5-year-old boy with rheumatic heart disease and subsiding rheumatic fever, had been a patient at the House of the Good Samaritan since July, 1945 — an interval of four months. Fifteen of the twenty-one cultures of the throat taken from August 1 to November 7 yielded Group A beta-hemolytic streptococci, Type 30. The child had large tonsils and cervical adenopathy. Twice during September and October he developed a profuse purulent nasal discharge, which also yielded beta-hemolytic strepto-

*Research assistant, Department of Preventive Medicine, and instructor, Department of Medicine, Yale University School of Medicine; formerly, resident physician, House of the Good Samaritan.

†Assistant in medicine, Harvard Medical School; associate director of research, House of the Good Samaritan.

‡Lecturer on medicine, Harvard Medical School (on leave of absence); director of research, House of the Good Samaritan (on leave of absence); medical director, Helen Hay Whitney Foundation, New York City.

cocci on culture, although there were no elevation of temperature and no other associated signs of illness. The serologic type of the isolated streptococci did not change.

On October 1 another small boy (Case 2) was admitted with the diagnosis of rheumatic fever, rheumatic heart disease and chorea. Three successive daily routine admission cultures and subsequent weekly ones were negative for hemolytic streptococci until October 25, when the patient was moved into a large ward in which the only other occupant was the patient discussed above. The distance between the beds was about 20 feet, and neither child was permitted out of bed. Cultures of the throat in Case 2, taken on October 29 and 30, were positive (1+ and 4+,* respectively) for

The other girl, M. S., was admitted late in August, looked well and had no signs or symptoms of rheumatic fever except for a subcutaneous nodule and intermittent elevation of the erythrocyte sedimentation rate. The throat cultures contained no hemolytic streptococci. In early October, J. R. was allowed out of bed for brief intervals with resulting direct contact with her wardmates, one of whom, M. S., developed throat cultures lightly positive for hemolytic streptococci, Type 28, with no signs or symptoms of acute streptococcal infection and with notable absence of fever. Within 2 weeks of the date of the first positive culture, however, erythema marginatum appeared and was followed by significant elevations in the antistreptolysin O titer and sedimentation

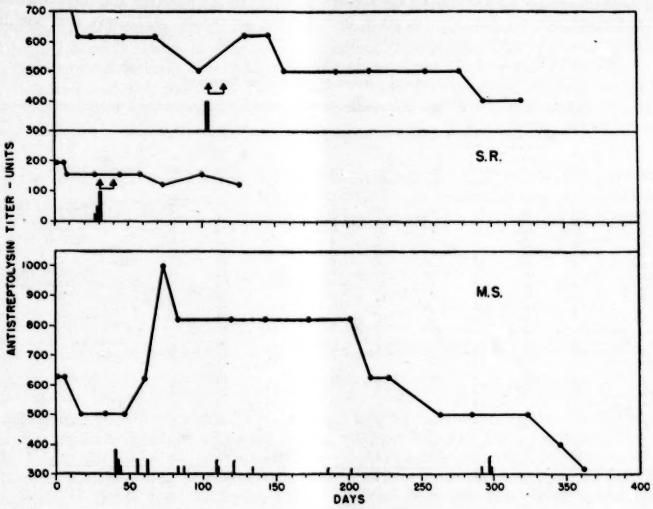

FIGURE 1. *Antistreptolysin Titers.*
The black columns represent positive throat cultures, the height of the column corresponding to the heaviness of the growth. The intervals of penicillin therapy are indicated by the arrows.

Group A, beta-hemolytic streptococci, Type 30, and on October 31 this child developed severe tonsillitis, with a maximum temperature of 105°F. Penicillin treatment was initiated within 4 hours of the onset of the clinical illness and continued in dosages of 10,000 units every 2 hours, being given intramuscularly for 10 days to a total of 1,200,000 units. A culture taken 18 hours after the beginning of the therapy, as well as all subsequent ones, contained no beta-hemolytic streptococci. The acute illness subsided promptly, and no recrudescence of rheumatic fever occurred. The other occupant of the room received penicillin in the same dosage for the same length of time, and although the culture became negative for hemolytic streptococci, the lymphadenopathy and tonsillar hypertrophy persisted.

CASE 3. J. R., one of two 7-year-old girls who occupied adjacent beds in a large ward, had been a carrier of beta-hemolytic streptococci, Type 28, as well as, occasionally, a second, untypable (X) strain, during the 7 months since admission in April, 1945. Of 43 throat cultures taken during that time, 38 were recorded as 1+ to 4+, with Type 28 predominating.

*Grades 1+ to 4+ represent increasing heaviness of growth of organisms on culture plates.

rate and by the development of many nodules, mild arthralgia, transient tendon contractures, hepatitis, later chorea and auscultatory and electrocardiographic evidence of heart disease, including pericarditis. The rheumatic syndrome persisted for months, during which the streptococci occasionally reappeared in the throat cultures (Fig. 1).

It is apparent that in these 2 cases hemolytic streptococci were transmitted from a chronic carrier to a susceptible person. In 1 case the streptococcal invasion caused a severe clinical respiratory infection, which, however, was not followed by a recurrence of rheumatic fever. In the other case the resulting streptococcal infection, although subclinical, precipitated a recrudescence of rheumatic fever.

PROCEDURE

All patients whose routine throat cultures yielded hemolytic streptococci were followed by means of

cultures taken at least three times a week until the presence of the carrier state was established — that is, until the number of positive cultures was shown to be well in excess of the number of negative cultures, with no tendency to diminish.

Any patient suffering from an acute streptococcal infection was placed under treatment with penicillin as soon as the diagnosis was made. A control culture was taken just before the first dose of penicillin. In such cases the treatment was identical with that given the healthy carriers.

Penicillin — in doses of 10,000 units every two hours, day and night, for ten days — was given intramuscularly to a total of 1,200,000 units to all patients in these two classifications.

The organism isolated in each case was grouped and typed by the Lancefield capillary precipitin technic,[19] and its sensitivity to penicillin determined.

Throat cultures were taken three times weekly during treatment, daily from one to two weeks after treatment and then with gradually decreasing frequency to a routine weekly schedule.

Antistreptolysin O titers and erythrocyte sedimentation rates were followed at bi-monthly intervals.

When tonsillectomy was clinically indicated in the penicillin-treated cases, it was performed after the rheumatic fever had subsided and was preceded by several daily throat cultures, the last immediately before operation. Cultures of the open tonsillar fossae were obtained during operation, and the tonsils were sectioned and cultured. The patients were given penicillin prophylactically, beginning immediately after operation and continuing until the operative wound was healed and there was no fever.

Results

The primary object of the experiment was achieved in most cases — that is, beta-hemolytic streptococci were eliminated from the throat cultures in 17 of 20 cases for the duration of the post-treatment observation periods, which ranged from twenty* to one hundred and forty-six days (Table 1). Of the seventeen organisms that yielded to treatment, fifteen belonged to Group A, whereas the extracts of two failed to precipitate with A, C or H serums (Cases 14 and 18). In 2 of the 3 unsuccessful cases (12 and 17) the organisms, not of Group A, were also morphologically atypical and weakly hemolytic; in the third, the organism was an untypable strain of Group A, which was unusually sensitive to penicillin in vitro. There was no known factor common to these three organisms by which they differed from the seventeen that yielded to treatment. In 2 patients (Cases 3 and 5) the cultures became positive a second time, but with organisms of types different from those originally recovered.

The downward trend of the antistreptolysin O titer was apparently unaltered by the treatment of chronic carriers with penicillin. In 2 cases of acute streptococcal infection (Cases 2 and 4), each treated

Table 1. *Effect of Penicillin Therapy.**

Case No.	Hemolytic Streptococcus		Sensitivity of Organism†	Pretreatment Cultures				Post-Treatment Cultures				Post-Tonsillectomy Cultures		
	Group	Type		Interval	No. Taken	No. Positive	Grade	Interval	No. Taken	No. Positive	Grade	Throat	Fossae	Tonsils
			units/cc.	*days*				*days*						
1	A	30	.01	99	21	15	0–4+	125	33	0		Negative	Negative	Negative
2	A	30	.006	3	3	3	1+–4+	102	40	0		—	—	—
3	A	28X	.008	190	43	38	0–4+	96	31	6		—	—	—
4	A	12	.02	2	2	2	4+	180	28	0		Negative	Negative	Negative
5	A	1	.02	24	14	12	0–3+	20	11	0		—	—	—
6	A	X	.008	23	20	16	0–3+	77	15	2	1+	—	—	—
7	A	5	.01	30	15	14	0–3+	185	43	0		Negative	Negative	Negative
8	A	X	.01	123	37	21	0–2+	150	32	0		Negative	Negative	Negative
9	A	X	.04	158	53	17	0–2+	35	7	0		—	—	—
10‡	A	5	.04	13	9	5	0–2+	140	22	0		—	—	—
11‡	A	5	.04	16	11	11	1+–4+	190	30	0		—	—	—
12	Unknown (not A, C or H)		.06	21	11	10	0–3+	29	10	7	1+–2+	—	—	—
13	A	19	.02	12	6	6	1+–3+	125	17	0		—	—	—
14	Unknown (not A, C or H)		.006 .02	23	12	7	0–2+	54	12	0		—	—	—
15	A	X	.006	22	12	8	0–1+	51	20	0		—	—	—
16	A	30	.02	14	8	5	0–2+	165	27	0		—	—	—
17	Unknown (not A, C or H)			14	8	6	0–1+	24	9	5	1+	—	—	—
18	Unknown (not A, C or H)		.008	62	19	17	0–3+	112	30	0		Negative	Negative	Negative
19	A	X	.008	16	15	13	0–2+	56	20	0		—	—	—
20	A	X	.02	4	4	4	3+–4+	146	22	0		—	—	—

*Penicillin dosage in each case, 10,000 units every two hours, for ten days to total of 1,200,000.
†Minimum inhibiting concentration of penicillin.
‡Sisters.

*Infection with a new type of streptococcus appeared on the twentieth post-treatment day in 1 case.

within two days of the appearance of the organism in the throat culture and within four hours of the onset of the clinical illness, there was no significant rise in the antistreptolysin titer (Fig. 1) and no recrudescence of rheumatic fever. In contrast, in another patient, M. S., who was not treated because the infection was subclinical, the antistreptolysin titer rose from 500 to 1000 units coincident with the development of multiple signs and symptoms of rheumatic fever. These observations suggest that a careful comparative study of penicillin-treated and untreated cases of streptococcal infection in patients with rheumatic fever should be undertaken.

In each of the 2 cases in which an organism was believed to have been transmitted from one patient to another, the streptococcus recovered from the recipient appeared to be more sensitive to penicillin than that of the carrier donor, although it is acknowledged that the differences are within the limits of error. In 1 case the inhibiting concentration of penicillin in vitro dropped from .01 to .006 units per cubic centimeter, and in the other, from .008 to .006 units on repeated determinations.

Tonsillectomy was performed in 5 of the treated cases. In each of these, cultures of the throat, tonsillar fossae and sectioned tonsils were negative for beta-hemolytic streptococci. It may be noted that the intervals between penicillin treatment and operation ranged from one hundred and twenty-five to one hundred and eighty-five days. It would be of importance to determine whether the complete eradication of hemolytic streptococci from the interior of the tonsils and the other deep tissues of the upper respiratory tract by means of penicillin had any influence on the chronicity of rheumatic fever.

Experience with Slowly Absorbable Penicillin

A program similar to that described above was undertaken at a convalescent home,* where repeated rounds of streptococcal infections had been troublesome.

Two sets of throat cultures of patients and personnel were obtained within a few days of one another, and in each case in which beta-hemolytic streptococci were found in one or both of these cultures, two additional cultures were obtained at intervals of a few days. Treatment was instituted in the 6 cases in which these preliminary cultures were positive.

Penicillin in beeswax and peanut oil was given to each of the selected patients intramuscularly in single daily doses of 150,000 units for ten days, to a total of 1,500,000 units. Throat cultures were taken at intervals of three or four days, beginning twenty-four hours after the first dose of penicillin — that is, just before the administration of the second dose. Serum penicillin concentrations were determined at specific intervals (Table 2).

These observations were necessarily less complete than those on patients in the House of the Good Samaritan because of the shorter hospitalization periods and the heterogeneous types of cases, as well as the geographical distance of the institution from the laboratory. None of the strains obtained from these patients was classifiable with available typing serums. In 5 cases the cultures remained free of hemolytic streptococci for the duration of the observation period (about one month); in the remaining case the culture again became positive, but whether the organism was of the same or different type could not be determined.

Table 2. *Results of Penicillin Therapy* in Repeated Streptococcal Infections at Wellesley Convalescent Home.*

Patient	Pretreatment Culture			Post-Treatment Cultures			Serum Penicillin Concentration		
	No. taken	No. positive	Grade	No. taken	No. positive	Grade	at 2 hr.	at 10-14 hr.	at 24 hr.
							units/cc.	*units/cc.*	*units/cc.*
D	3	3	2+-4+	5	0	—	0.2	0.03	0.012
									<0.012
G	3	3	1+-4+	5	0	—	—	0.075	<0.012
N	3	3	1+-3+	7	0	—	0.015	0.03	<0.012
C	4	3	0-4+	3	0	—	0.3	0.02	<0.012
M	3	3	2+-4+	6	2	0-2+	0.2	0.12	0.015
								0.15	
A	3	3	3+-4+	3	0	—	0.2	<0.012	—

*Penicillin in beeswax and peanut oil given intramuscularly in single daily doses of 1,500,000 units for ten days, to total of 1,500,000 units.

Summary

Eighteen chronic carriers of beta-hemolytic streptococci and 2 cases of acute streptococcal tonsillitis were treated with a total of 1,200,000 units of penicillin each, given intramuscularly during ten days.

In 17 cases the infecting organisms were eliminated permanently from the throat cultures. One Group A streptococcus and two that did not belong to Group A, C or H failed to disappear.

In 5 cases in which tonsillectomies were performed one hundred and twenty-five to one hundred and eighty-five days after treatment, the tonsillar fossae and sectioned tonsils were free from hemolytic streptococci.

*The Wellesley Convalescent Home, through the courtesy of Dr. Henry Gallup.

In 2 cases the antistreptolysin O titers did not rise after acute streptococcal infections that were promptly treated with penicillin.

Penicillin injections once daily for ten days in slowly absorbable form were observed to be successful in eliminating the beta-hemolytic streptococcus carrier state in 5 of 6 cases.

The ability to eliminate beta-hemolytic streptococci from the throats of most patients in close contact with persons who have had rheumatic fever suggests a practical method of protecting the latter group from beta-hemolytic streptococcus infection.

It is evident that further observations are needed to ascertain whether prompt penicillin treatment for acute hemolytic streptococcus infections in subjects with rheumatic fever may decrease the likelihood of a recurrence of rheumatic fever.

References

1. Commission on Acute Respiratory Diseases. Study of food-borne epidemic of tonsillitis and pharyngitis due to β-hemolytic streptococcus, Type 5. *Bull. Johns Hopkins Hosp.* **77**:143-210, 1945.
2. Harrison, F. F., and Miller, J. K. Problem of hemolytic streptococcus carriers in hospital personnel. *War Med.* **8**:333-336, 1945.
3. Julianelle, L. A., and Siegel, M. Epidemiology of acute respiratory infections conditioned by sulfonamides. II. Gross alterations in nasopharyngeal flora associated with treatment. *Ann. Int. Med.* **22**:10-20, 1945.
4. Rubenstein, A. D., and Foley, G. E. Effect of chemotherapy on duration of carrier state following scarlet fever. *New Eng. J. Med.* **233**:315-322, 1945.
5. Editorial. Dangers of chemoprophylaxis. *New Eng. J. Med.* **234**: 487-489, 1946.
6. Hamburger, M., Jr., Mattman, L. H., Grosch, D. S., and Hurst, V. Susceptibility to sulfadiazine of hemolytic streptococci in Army camps. *Am. J. Med.* **1**:23-27, 1946.
7. Plummer, N., Duerschner, D. R., Warren, H. D., Rogliano, F. T., and Sloan, R. A. Penicillin therapy in hemolytic streptococcic pharyngitis and tonsillitis. *J. A. M. A.* **127**:369-374, 1945.
8. Keith, J. D., Maclennan, J., Williamson, J., Carpenter, J., and Armstrong, C. Penicillin in haemolytic streptococcal infections of throat. *Canad. M. A. J.* **53**:471-478, 1945.
9. Meads, M., Flipse, M. E., Jr., Barnes, M. W., and Finland, M. Penicillin treatment of scarlet fever: bacteriologic study of nose and throat of patients treated intramuscularly or by spray with penicillin and comparison with sulfadiazine. *J. A. M. A.* **129**: 785-789, 1945.
10. Hamburger, M., Jr., and Lemon, H. M. Problem of dangerous carrier of hemolytic streptococci. III. Chemotherapeutic control of nasal carriers. *J. A. M. A.* **130**:836-841, 1946.
11. Spink, W. W., Rantz, L. A., Boisvert, P. L., and Coggeshall, H. Sulfadiazine and penicillin for hemolytic streptococcus infections of upper respiratory tract: evaluation in tonsillitis, nasopharyngitis and scarlet fever. *Arch. Int. Med.* **77**:260-294, 1946.
12. Rantz, L. A., Spink, W. W., Boisvert, P. L., and Coggeshall, H Treatment of rheumatic fever with penicillin. *J. Pediat.* **26**:576-582, 1945.
13. Watson, R. F., Rothbard, S., and Swift, H. F. Use of penicillin in rheumatic fever. *J. A. M. A.* **126**:274-280, 1944.
14. Foster, F. P. et al. Treatment of acute rheumatic fever with penicillin. *J. A. M. A.* **126**:281, 1944.
15. Rantz, L. A., Boisvert, P. L., and Spink, W. W. Hemolytic streptococcal sore throat; antibody response following treatment with penicillin, sulfadiazine, and salicylates. *Science* **103**:352, 1946.
16. Epidemiology Unit No. 82. Observations on treatment of scarlet fever with penicillin. *Am. J. M. Sc.* **211**:417-420, 1946.
17. Jennings, R., and DeLamater, E. D. Penicillin therapy of scarlet fever and streptococcus carrier. *Am. J. Med.* **2**:1-22, 1947.
18. Hirsh, H. L., Rotman-Kavka, G., Dowling, H. F., and Sweet, L. K. Penicillin therapy of scarlet fever: comparison with antitoxin and symptomatic therapy. *J. A. M. A.* **133**:657-660, 1947.
19. Swift, H. F., Wilson, A. T., and Lancefield, R. C. Typing group A hemolytic streptococci by M precipitin reactions in capillary pipettes. *J. Exper. Med.* **78**:127-133, 1943.

THE VALUE OF THE METHYLENE BLUE TEST IN THE DETECTION OF BILIRUBIN*

C. Lawrence Holt, M.D.†

PORTLAND, MAINE

WHEN Fellinger and Menkes[1] described a modification of Franke's[2] methylene blue test for bile in the urine, they suggested that certain quantitative potentialities of the test existed. They observed that determinations made on twenty-four-hour collections of urine paralleled blood bilirubin levels to a satisfactory degree. Determinations on individual samples, however, were not reliable, since dilution factors, as represented by varying specific gravities of the urine, affected the depth of color that took place after the addition of methylene blue. The depth of color in their technic represented the basis of quantitative interpretation.

Gellis and Stokes,[3] after considerable investigative studies, reported a further modification of the original test. They suggested that it might be used as an aid in the early recognition of bilirubinuria in infectious hepatitis. The authors did not claim to describe an unusually sensitive or accurate test for the presence of bilirubin but rather to suggest that the test could be used for demonstrating bilirubinuria in working with large numbers of soldiers in the field.

The present investigation was undertaken to determine the accuracy and reliability of the test as judged by civilian medical standards, in an effort to determine whether it has any place in routine laboratory procedures. The technic used was that described by Stokes and Gellis.[3, 4] This consisted of a drop by drop addition, to 5 cc. of urine, of an aqueous methylene blue solution (0.2 per cent by actual dye content) from a 1-cc. pipette delivering 20 drops per cubic centimeter. If 5 or more drops were necessary to change the green color of the mixture of urine and methylene blue to a blue color, the test was considered positive for bilirubinuria.

Investigators at the Boston City Hospital[5] found that chrome pigments other than bilirubin gave a greenish color when methylene blue was added and therefore believed that the test was not specific. Other workers had previously made the same observation.[6, 7] Roch,[7] indeed, offered this lack of specificity as a criticism of Franke's original test. Figge's[8] criticism was of a similar nature, and appeared in print shortly after Myers[8] had reported

*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Formerly, assistant in medicine, Boston University School of Medicine, and fellow in internal medicine, Evans Memorial, Massachusetts Memorial Hospitals.

that he had adapted the test as an early demonstration of toxic hepatitis resulting from industrial toxins. Recent spectrophotometric studies made by a group at the Mayo Clinic[9, 10] demonstrated that the color changes involved in the test were unquestionably due to a blending of blue and yellow colors, rather than to some specific chemical reaction between methylene blue and bilirubin. In general medical practice there are several chrome pigments that might interfere with the accuracy of the test. Two of these, penicillin and riboflavin, were chosen for study because of their present popularity as therapeutic agents. Patients receiving these substances were studied in some detail to determine how much of the substances was necessary to cause a yellowish discoloration of the urine sufficient to give a falsely positive test on the addition of methylene blue.

Studies were first made on a group of 14 patients receiving less than 300,000 units of penicillin in twenty-four hours. Urinalyses showed that the methylene blue test may give reliable results (Table 1), so long as the specific gravity of the urine is not unusually high. As demonstrated below in detail, the deeper color of the more concentrated urines may give a falsely positive reaction with methylene blue.

Studies of urine in patients receiving more than 600,000 units of penicillin in twenty-four hours gave three borderline and one distinctly falsely positive methylene blue tests. The Harrison and spot diazo tests,[11] however, indicated that these specimens contained no bilirubin. The foam test in these cases was positive and hence misleading.

Studies on 4 patients receiving large amounts of components of the vitamin B complex or moderate amounts of pure riboflavin (3 to 5 mg.) revealed falsely positive tests with methylene blue in 3 cases and a borderline reading in 1. The foam test was positive in all cases. The Harrison and spot diazo tests, however, were negative. It is apparent, therefore, that both riboflavin and penicillin may give falsely positive foam and methylene blue tests.

The effect on the methylene blue test of concentration of chrome pigments in the urine was clearly demonstrated by a study of samples of urine with varying specific gravities from a patient receiving 900,000 units of penicillin daily. The results are recorded in Table 2. Urines with low specific gravities (1.003 to 1.006) required but 1 drop of

TABLE 1. *Penicillin-Containing Urines (from Patients Receiving less than 300,000 Units) in 6-a.m. Specimens.*

Diagnosis	Penicillin Dosage	Specific Gravity	Foam Test	Harrison Test	Methylene Blue Test
	units				
Syphilis, primary; Herxheimer reaction*	160,000	1.016	++	±	4
Otitis media; myocardial infarct	160,000	1.006	0	0	1
Bronchopneumonia, diabetes and arteriosclerotic heart disease, with failure; hepatomegaly	90,000	1.011	+	0	3
Diabetes; ulcer with cellulitis	200,000	1.015	0	0	1
Empyema and pneumonia	160,000	1.008	0	0	1
Keratodermatitis; cellulitis of legs	160,000	1.016	0	0	1
Syphilis, secondary; chancroid	160,000	1.030	±	0	3
Syphilis, primary	160,000	1.027	±	0	2
Osteomyelitis; amyloid disease	300,000	1.010	0	0	1
Bronchopneumonia, diabetes and arteriosclerotic heart disease with failure; hepatomegaly	90,000	1.012	±	0	1
? Gall-bladder disease†	120,000	1.010	+++	+++	11
Diabetic gangrene	120,000	1.007	0	0	1
Carcinoma of sigmoid, with abscess	120,000	1.006	0	0	1
Sprue, hematoma and bleeding tendency	120,000	1.008	±	±	2

*In this case the patient had just had a moderately severe Herxheimer reaction, which might have accounted for the borderline bilirubinuria as shown by the Harrison test.

†In this case the patient was later proved to have an empyema of the gall bladder and undoubtedly had a regurgitation type of jaundice due to edema of the biliary passages.

TABLE 2. *Comparison of Methylene Blue Test with Depth of Pigment Color in Urine Containing Penicillin.**

Date	Time of Passage of Sample	Methylene Blue	Specific Gravity	Colorimeter†	
		drops		"G" values	"L" values
2/18 —	11:00 a.m.	4	1.015	70	.1503
	12:00 p.m.	2	1.012	77	.1135
2/19 —	7:30 a.m.	1	1.006	83	.0796
	2:00 p.m.	2	1.012	75	.1235
	4:30 p.m.	1	1.003	87	.0568
2/22 —	8:00 a.m.	4	1.017	69	.1565

*Patient received 900,000 units in twenty-four hours.
†Evelyn — 440 filter.

TABLE 3. *Representative Samples, Showing Effect of Reaction on Methylene Blue Test.*

Methylene Blue	Reaction	Methylene Blue	Reaction
3	pH4	13	pH1
4	pH5	13	pH3
4	pH6	13	pH4.5
4	pH7	13	pH6
4	pH8	15	pH9

methylene blue to complete the appearance of a blue color. Urines with higher specific gravities (1.015 to 1.017) required 4 drops of methylene blue to give a positive test. Accurate comparisons of the depth of color of these specimens were made with the Evelyn colorimeter using a 440 filter. The range in values obtained paralleled quite closely the range in specific gravities of the specimens. This not only is further corroborative evidence that the methylene blue test depends on a physical blending of pigments but also substantiates the findings of Fellinger and Menkes,[1] who demonstrated the influence of specific gravity on the methylene blue test.

The effect of the reaction on the methylene blue test was studied, and the results are reported in Table 3. The changes in reaction were made by the addition of varying amounts of acetic acid and sodium hydroxide to the specimens of urine to be tested. In 1 case urine from a jaundiced patient was tested. In another the tests were made on a specimen of normal urine to which pure bilirubin was added. There was a slight tendency for more methylene blue to be required in the more alkaline solutions (Table 3), but not enough to be considered a real factor.

TABLE 4. *Comparison of Tests for Bile in the Urine.*

DILUTION	FOAM TEST	METHYLENE BLUE TEST	HARRISON TEST	SPOT DIAZO TEST	WATSON TEST	NAUMANN MODIFICATION OF SPOT DIAZO TEST	NAUMANN MODIFICATION OF HARRISON TEST	IODINE TEST
1:2	++++	6	++++	+++	++++	−	−	+
1:4	+++	4	++++	++	++++	−	−	+
1:8	++	2	+++	++	+++	−	−	±
1:16	+	1	++	++	++	−	−	±
1:32	+	1	+	+	+	−	−	0
1:64	±	1	+	+	+	−	−	0
1:128	0	0	+	+	0	+	+	0
1:256	0	0	0	trace	0	+	+	0

TABLE 5. *Penicillin-Containing Urines in Patients Receiving More Than 600,000 Units (6-a.m. Specimens).*

DIAGNOSIS	PENICILLIN DOSAGE	SPECIFIC GRAVITY	FOAM TEST	HARRISON TEST	METHYLENE BLUE TEST
	units				
Rheumatic heart disease and subacute bacterial endocarditis	625,000	1.003	0	0	1
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.014	++	0	3
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.008	++	0	4
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.012	++	0	4
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.010	+++	0	6
Rheumatic heart disease and subacute bacterial endocarditis (2 p.m.)	900,000	1.005	0	0	1
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.014	++	0	4

TABLE 6. *Urine* from Patients Taking Large Doses of Vitamin B Compounds or Relatively Small Amounts of Pure Riboflavin.*

CASE NO.	FOAM TEST	HARRISON TEST	SPOT DIAZO TEST	METHYLENE BLUE TEST
1	++	±	±	5
2	++	0	0	6
3	++	0	0	5
4	++	0	0	4

*Representative samples of urine tested one to four hours after oral administration of riboflavin.

To compare the relative sensitivity of the methylene blue and other popular tests for bilirubinuria, determinations of serial dilutions of a specimen of urine from a jaundiced patient were made. The results are recorded in Table 4. The Naumann[12] concentration test is certainly the most sensitive, and may in fact demonstrate the presence of bilirubin in normal urine. The Harrison,[11] the Watson[13] modification of the Harrison and the spot diazo tests,[11] although less sensitive than the Naumann concentration test, are reliable and excellent. The foam test, if carried out under daylight and compared with a control urine, is found to be quite sensitive but also extremely nonspecific, since it will give a falsely positive test in the presence of riboflavin, penicillin and quinacrine (Atabrin). All these tests are considerably more sensitive than the methylene blue procedure.

There are three approaches to the problem of determining the actual concentration of bilirubin that must be present for the methylene blue test to be positive. One is to add various known amounts of bilirubin* to urine. Another is to make serial dilutions of urine from a jaundiced patient and to determine the amount of bilirubin present in the greatest dilution giving a positive test. A third method is to determine the total bilirubin content of serum from a jaundiced patient and to determine how much of this serum must be added to measured amounts of urine to give a positive test. It is not the purpose of the present paper to discuss the relative merits or disadvantages of these methods; difficulties and uncertainties are encountered in all of them. Exact quantitative recoveries could not be made when known amounts of bilirubin were added to specimens of urine, regardless of whether bilirubin was added as an alkaline solution, as alkaline chloroform solution[14] or as solution prepared in accordance with the more complicated technic of Grotepass and van den Bergh.[15] The methods for determining the bilirubin content of urines from jaundiced patients were likewise unsatisfactory. Consistent results could not be obtained with Hunter's[16] technic or Godfried's[11] modification of it. In the present study a modification of Godfried's technic was devised so that the final result could be determined by the Evelyn colorimeter, but this also proved disappointing. The third method, although it also has certain drawbacks, gave the most satisfactory and consistent results. The methylene blue test, by the use of this method, was positive when 2 or 3 mg. per 100 cc. (average of 2.5 mg. per 100 cc.) of bilirubin was present.

Although the methylene blue test is neither specific nor sensitive, it is of definite value in giving a roughly quantitative index of the daily trend of icterus in a jaundiced patient. It obviates the necessity of multiple venipunctures, which are required for blood bilirubin determinations. It is the only test to date for bilirubin that can be quantitated in unit measures — that is, in drops. The recently described semiquantitative test of Watson and Hawkinson,[17] using their modification of the Harrison spot test and a standard color chart, is not so quantitative as the methylene blue test. Daily variations in the methylene blue test can be kept at a minimum by testing prebreakfast specimens (Table 5). In this manner, changes in the specific gravity will not be great. More accurate determinations may be made on twenty-four-hour collections, provided that the urine is kept in a cool, dark place, preferably in a receptacle whose bottom is covered with a thin layer of mineral oil. Penicillin and riboflavin will not interfere with the daily determinations of bilirubinuria by the methylene blue test, since in most cases the patient will receive a constant dose of these drugs and excrete a constant amount from day to day (Table 6). The procedure is therefore considered to be of definite value.

*Eastman Kodak preparation used in present study.

Summary

Evaluation of the methylene blue test for bilirubinuria has yielded the following results. The test is nonspecific and may give falsely positive results when the urine contains yellow pigments, such as penicillin and riboflavin. The test is not significantly affected by changes in the urinary reaction, but is affected by changes in the specific gravity. The test is less sensitive than the Naumann concentration test, the Harrison, the spot diazo and the Watson modification of the Harrison and the foam tests. The Naumann concentration test, however, may give positive results in normal urines, and the foam test is highly nonspecific. The present study suggests that the methylene blue test is positive when the concentration of bilirubin in the urine is 2 or 3 mg. per 100 cc. or more. Although the test is neither highly accurate nor specific, it provides a valuable means for estimating the daily excretion of bilirubin in the urine of jaundiced patients.

29 Deering Street

References

1. Fellinger, K., and Menkes, K. Über quantitative Bilirubinbestimmungen im Harn mit der Methylenblaumethode. *Wien. klin. Wchnschr.* **46**:133, 1933.
2. Franke, K. Methylenblau, ein einfaches sehr empfindliches Reagens zum Nachweis von Bilirubin. *Med. Klin.* **27**:94-96, 1931.
3. Gellis, S. S., and Stokes, J., Jr. Methylene blue test in infectious (epidemic) hepatitis. *J. A. M. A.* **128**:782, 1945.
4. Gellis, S. S., Neefe, J. R., Reinhold, J. G., and Stokes, J., Jr. Methylene blue test for bilirubin in urine. *J. A. M. A.* **128**:826, 1945.
5. Watson, J., Meads, M., and Castle, W. B. Tests for urinary bilirubin. *J. A. M. A.* **128**:308, 1945.
6. Figge, F. H. J. Green color of methylene blue-bilirubin mixture. *J. A. M. A.* **128**:613, 1945.
7. Roch, M. Über Methylenblau als Reagens zum Nachweis von Bilirubin. *Med. Klin.* **27**:589, 1931.
8. Myers, C. P. Use of methylene blue in testing for bilirubin in urine. *J. Indust. Hyg. & Toxicol.* **27**:52-55, 1945.
9. Stokes, G. D., Gambill, E. E., and Osterberg, A. E. Methylene blue test for bilirubinuria: clinical and spectrophotometric observations. *Proc. Staff Meet., Mayo Clin.* **21**:267-269, 1946.
10. *Idem.* Methylene blue test for bilirubinuria: clinical and spectrophotometric observations. *J. Lab. & Clin. Med.* **31**:924-933, 1946.
11. Godfried, E. G. Clinical tests for bilirubin in urine. *Biochem. J.* **28**: 2056-2060, 1934.
12. Naumann, H. N. Studies on bile pigments. II. New test for bilirubin in urine and its use for detection of bilirubin in normal urine. *Biochem. J.* **30**:762-764, 1936.
13. Hawkinson, V., Watson, C. J., and Turner, R. H. Modification of Harrison's test for bilirubin in urine especially suited for mass and serial usage. *J. A. M. A.* **129**:514, 1945.
14. Rabinowitch, I. M. Renal threshold of bilirubin. *J. Biol. Chem.* **97**:163-175, 1932.
15. van den Bergh, A. A. H., and Grotepass, W. Improved method for determination of bilirubin in blood. *Brit. M. J.* **1**:1157-1159, 1934.
16. Hunter, G. Diazo-method for detecting bilirubin in urine. *Canad. M. A. J.* **23**:823, 1930.
17. Watson, C. J., and Hawkinson, V. Semiquantitative estimation of bilirubin in urine by means of barium-strip modification of Harrison's test. *J. Lab. & Clin. Med.* **31**:914, 1946.

MEDICAL PROGRESS

GENERAL PRINCIPLES OF THE LABORATORY DIAGNOSIS OF VIRAL INFECTIONS*

F. S. CHEEVER, M.D.†

BOSTON

VIRUSES may be defined as ultramicroscopic agents, usually filterable, that are unable to propagate themselves in the absence of living cells and that are frequently the cause of clinical disease in man. This definition does not set off viruses sharply from certain bacteria; in fact, the current view is that "viruses represent the degenerate descendants of larger pathogenic micro-organisms."[1] Laboratory procedures for the specific diagnosis of disease due to bacterial agents are well known and standardized, and can usually be handled satisfactorily by the average hospital laboratory. The identification of virus agents, which is carried out along the same general lines, is rendered difficult by certain characteristics of these agents. The more important of these properties are as follows.

Virus agents range in size from approximately 10 (as in foot and mouth disease and poliomyelitis) to 250 millimicrons or more in diameter (as in psittacosis). Although a few of the larger viruses may be seen with the ordinary microscope, the great majority are too small for its resolving powers. Typical morphology, staining reactions and so forth, which are important in diagnostic bacteriology, are not yet available for the recognition of most viruses.

Virus agents are obligate intracellular parasites, and multiplication does not take place in the absence of living cells. Thus, for their propagation, recourse must be had to tissue culture, animal inoculation or the use of the developing chick embryo. These methods are complicated, expensive and protracted compared to those available for the culture of bacterial agents.

Although, broadly speaking, the resistance of viruses to various chemical and physical forces parallels that shown by the vegetative forms of the majority of pathogenic bacteria, it is characteristic of many of the former agents that their extracellular survival time is relatively brief except under special conditions. For example, cultures of many pathogenic bacteria retain their viability for long periods under varying conditions of temperature if inoculated on agar slants protected from the effects of evaporation. Such a technic permits the shipping of pathogenic cultures from all parts of the world to central laboratories for identification. Unfortunately, no such easy method is available in the identification of virus agents. To maintain their viability in the absence of actively proliferating tissue cells, one must resort to freezing at —70°C. or lyophilization or, less satisfactorily, preservation in 50 per cent glycerol. This makes the problem of transporting or shipping virus agents for any distance a difficult one. This question is discussed in greater detail below.

*From the Department of Bacteriology and the Department of Immunology, Harvard Medical School.

†Assistant professor of bacteriology and immunology, Harvard Medical School.

DIAGNOSTIC PROCEDURES

Diagnostic procedures for viral infections may be discussed under the following general headings: isolation and identification of the virus itself; serologic demonstration of the formation of specific antibodies against a virus during the clinical course of the disease; pathological demonstration of specific inclusion bodies; and skin tests illustrating the development of altered skin sensitivity to a specific virus or some fraction of it as a result of infection with the specific agent.

Although in a few virus diseases it is at least theoretically possible to make a specific diagnosis by several of these methods, in general, only one procedure is used for routine diagnostic work. In the majority of cases the serologic approach is the most practical one. The disadvantage of this method is that the diagnosis is made in retrospect, rather than in the early stages of the patient's illness.

Isolation of the Virus Agent

The isolation of the causative virus agent from a patient and its subsequent identification is usually a costly, laborious and prolonged procedure, hardly practical for use by other than the specialized laboratory. Animal inoculation and injection of the developing chick embryo are the two methods generally used. Mice, hamsters, guinea pigs, ferrets, rabbits and monkeys are the animals most frequently employed.

If the material to be inoculated is uncontaminated by bacterial agents (as in blood or spinal fluid), it may be injected directly into the animal or chick embryo. Material such as tissue is washed with sterile water, weighed and cut into small pieces under aseptic conditions. It is ground in a sterile mortar with sterile sand or alundum and enough buffer solution or broth added to form a 20 per cent

suspension. (Physiologic saline solution appears to have a deleterious effect on some viruses.) The suspension is centrifuged at a low speed to throw down the coarser particles, and the supernatant fluid is used for injection.

In the event that the material to be inoculated is not free of bacterial agents, it must be suitably treated to obtain a bacterium-free inoculum. Filtration is effective for this purpose. Berkefeld, Mandler and Seitz filters are often used. In each a filter with a pore size sufficiently fine to hold back ordinary bacteria is employed; care must be taken not to reduce the porosity to a point where virus agents of larger sizes would also be held back. Other factors as well as particle size are important in determining the filtrability of an agent: the amount of positive or negative pressure applied, and the length of time over which it is exerted, the type and reaction of the suspending fluid and the electrical charge of the filter and of the fluid to be filtered. The presence of larger tissue particles in the suspending fluid results in the rapid clogging of the pores, and for this reason the fluid should be cleared first by centrifugation at a moderate speed (3000 to 4000 r.p.m. for thirty to sixty minutes) or by preliminary filtration through filter paper, or by a combination of both methods. Even under favorable circumstances, however, filtration results in a drop in virus titer in most cases.

Chemicals have been used to some extent in rendering suspensions bacteria free. Ether is occasionally used, particularly in work with the virus of poliomyelitis,[3] which is relatively resistant to the action of this agent. Similarly, Zephiran (a synthetic detergent) has been used for the isolation of bacteriophages[3] and of the influenza virus.[4]

Antibiotics, which are frequently employed in conjunction with chemotherapeutic agents such as the sulfonamides, are particularly useful in the inoculation of embryonated egg. Hirst[5] developed the technic of amniotic inoculation of unfiltered penicillin-treated throat washings from patients with influenza as a means of isolating the specific virus. If streptomycin or sulfadiazine is added as well the results are even better, and this method is fully as sensitive as animal inoculation. This work has recently been extended to mumps.[6] Nevertheless, animal inoculation continues to be widely used for the primary isolation of virus agents, whereas the chick embryo plays an important role in the propagation of the virus after its adaptation by animal passage.

Once isolated, the virus may be identified by the production of specific pathologic lesions in the experimental animal or by appropriate serologic technics — that is, by complement fixation, virus neutralization, precipitation-flocculation or hemagglutination-inhibition tests with specific antiserums. These tests are considered below in greater detail.

Serologic Diagnosis

Viral infections in man usually stimulate the production of specific antibodies against the invading virus. The demonstration of these antibodies by proper serologic technics offers presumptive evidence of past or present infection with the specific agent. This evidence is particularly valuable if it can be shown that the antibodies developed during the course of the patient's illness, since such a finding usually offers convincing proof of the causal relation between the clinical disease and the specific virus. The basic principle is analogous to that underlying the serologic diagnosis of bacterial infections. For both groups of diseases it is frequently impractical to isolate and identify the causative agent, and recourse must be had to diagnosis by the indirect means of demonstrating the appearance or rise in titer of specific antibodies during the course of the infection. This is particularly true in cases of viral infections of the central nervous system, as recently emphasized by Rivers,[7] who points out the difficulty of isolating the causative agent from the blood or spinal fluid.

As in diseases of bacterial origin, the results obtained from the examination of a single specimen of serum in any given case rarely permit a final diagnosis. The demonstration of a significant antibody titer against a specific virus in a single serum specimen simply means that the patient has at some time been infected with that particular agent. There is no assurance that the present illness is causally connected with the occurrence of these particular antibodies, since clinical or subclinical infection in the past may well have been the specific stimulation for their production. In certain cases, — for example, in mumps, — however, when a high titer of antibody such as is characteristic of persons who have recently recovered from the specific disease is found in a single specimen, it may be regarded as highly suggestive or presumptive evidence of the nature of the infection, although an increase in titer cannot be demonstrated. But, as in bacterial infections, to obtain a conclusive serologic diagnosis it is always necessary to demonstrate a significant rise in antibody titer during the course of the disease. Thus, at least two specimens of serum should be examined: one drawn as soon as possible after the onset of clinical signs and symptoms and the other approximately two or three weeks later. Usually, this interval between the drawing of specimens during the acute and convalescent phases is long enough to permit a significant rise in antibody titer to be detected. The most important exception is in the demonstration of neutralizing antibodies; these frequently appear later than the others, and if this technic is to be applied a third specimen of serum should be drawn six to eight weeks after the onset of the disease.

Table 1 presents the frequent combinations of reactions with serums drawn during the acute and convalescent phases and the conclusions that one is justified in drawing from them.

Serologic reactions for the identification of virus agents present particular technical difficulties in the preparation of the antigens. Since viruses cannot be propagated in the absence of living cells, the preparation of viral antigens free from troublesome tissue components is usually difficult and sometimes impossible. The viral antigen usually consists of an extract of parasitized cells. In setting up a test it is necessary to include a control consisting of an extract of normal tissue prepared in exactly the same way. If a viral antiserum — prepared by the injection of a suitable animal with tissue cells containing the virus — is employed, the viral antigen used in the actual test should be prepared from infected heterologous cells if possible. These technical difficulties render the serologic diagnosis of viral diseases more complicated and protracted than the process of applying the analogous tests to diseases of bacterial origin.

Four general types of serologic reactions are used for the practical diagnosis of viral infections: virus neutralization; complement fixation; agglutination or flocculation, or both; and hemagglutination inhibition. The first two find wide application in a variety of diseases, but they are relatively expensive and require time. The third, which can be applied only to the largest virus agents, is limited to variola-vaccinia for all practical purposes. At present the fourth is applicable to influenza and perhaps to mumps; the speed and ease with which it can be carried out, however, give it a distinct technical advantage over the others.

Neutralization tests. Many viral infections stimulate the production of neutralizing antibodies on the part of the host during the course of the illness. These antibodies acquired their name from their ability to neutralize the disease-producing qualities of the specific virus, as evidenced by the inability of the serum-virus mixture to cause recognizable disease when inoculated into susceptible animals. They are associated with the globulin fraction of serum; the role of complement in this reaction remains uncertain. Mice are the test animals generally used. Although the results of the test on a single specimen of serum occasionally yield presumptive evidence that the disease in question is due to a specific virus, it is usually necessary to demonstrate a rise in the neutralizing antibody titer before a definite diagnosis can be made. Thus, the test must be run simultaneously on two specimens of serum: one drawn as soon as possible after the onset of the illness, and the other drawn four to six weeks later.

TABLE 1. *Combinations of Reactions, with Their Interpretations.*

COMBINATION	SERUM DRAWN DURING ACUTE PHASE	SERUM DRAWN DURING CONVALESCENT PHASE	CONCLUSION
1	Negative	Negative	Disease not due to virus tested
2	Negative	Positive	Disease presumably due to virus tested
3	Positive	Positive (significant rise in titer)	Disease presumably due to virus tested
4	Positive	Positive (no significant rise in titer)	1 — contact with the virus tested sometime in past, with no relation to present illness; 2 — first serum drawn too late in course of disease; 3 — second serum drawn too early in course of the disease.
5	Not tested	Negative	Disease not due to virus tested
6	Not tested	Positive	Interpretation impossible, unless titer of second specimen is at least as high as that usually found in persons recently recovered from the disease in question; in such cases a presumptive serologic diagnosis may be made on the basis of these suggestive findings.

The test is usually carried out with a constant amount of virus and varying dilutions of serum, although the reverse — serial dilutions of virus mixed with a constant amount of serum — may be employed, and is particularly useful in the study of neurotropic viruses. Serial dilutions of the serums from the acute and convalescent phases are set up in parallel, and a constant amount of virus is added to each tube. After the incubation of the virus-serum mixtures, susceptible animals are inoculated with samples from each and carefully followed for the development of the experimental disease. In a positive test serum drawn from the convalescent phase shows a significantly enhanced neutralizing or protective effect as compared to that of the acute phase.

This test has been particularly useful in the diagnosis of diseases of the central nervous system due to neurotropic viruses (lymphocytic chorio-meningitis[8] and the various encephalitides[9–12]). With the exception of poliomyelitis the test animal generally employed is the mouse, and the route of inoculation intracerebral, or occasionally intraperitoneal. Survival of a significant number of mice injected with a

serum-virus mixture is evidence of the presence of neutralizing antibodies, since the amount of virus in the mixture is such that if injected alone it would result in the death of all the mice. In poliomyelitis the monkey has been used as the test animal,[13, 14] but the multiplicity of the virus strains that cross react weakly if at all render this test impractical for routine diagnostic work.

This test is often applied in the diagnosis of viral infections caused by agents other than the strictly neurotropic ones. Theiler's[15] discovery that mice are susceptible to the intracerebral inoculation of the virus of yellow fever led to Sawyer's[16] application of the neutralization test in survey work. In influenza the virus-serum mixture is inoculated intranasally into a lightly anesthetized mouse.[17] At the end of seven days surviving mice are sacrificed and autopsied, and the lungs are examined for evidence of pulmonary consolidation. The neutralizing antibody content of antivaccinial[18] and antiherpes[19, 20] serums can be estimated by the inoculation of suitable mixtures of virus and immune serum on to the chorioallantoic membrane of the developing chick embryo and by the observation of the reduction in pox produced as compared to the number that develop after the inoculation of similar mixtures of virus and normal serum.

Complement-fixation tests. The viral agents causing infectious disease in man generally possess the property of stimulating the production of specific complement-fixing antibodies in the host as a sequel to infection. As such, the formation of these antibodies is entirely analogous to what happens in the course of infectious disease due to bacterial or protozoal agents, and the principles of the methods used for the detection of these antibodies are entirely similar. To establish an unequivocal diagnosis it is essential to prove that antibodies appear or show a significant rise in titer during the course of the infection. Hence at least two specimens of serum from each patient must be examined: one taken as soon as possible after onset, and the other drawn some days later. Since in some diseases the antibody response may occur as early as five days or as late as five weeks after onset, it may be necessary to test three specimens — during the acute phase, one or two weeks after onset and five or six weeks after onset. In a disease such as influenza A or B in which the antibody response is prompt (frequently within a week) and regular the first two specimens usually suffice.

The antigens employed represent the virus agents or their products. The source is frequently infected animal tissue: monkey parotid gland in mumps,[21–23] mouse brain[24, 25] or guinea-pig spleen in lymphocytic choriomeningitis,[26, 27] mouse brain in the various encephalitides,[24, 25, 27] mouse lung in influenza,[28–30] yolk sac in lymphogranuloma venereum[31] and psittacosis,[32] amniotic membrane in mumps[33] and allantoic fluid in influenza.[34] In at least three diseases — lymphocytic choriomeningitis,[26] influenza[35] and vaccinia[36] — soluble antigens capable of fixing complement in the presence of the specific antibodies have been isolated from infected tissues.

It has been pointed out that since viruses cannot be cultivated on lifeless mediums, infected tissues or body fluids must be depended on as sources of antigen. In certain diseases — notably in poliomyelitis — the virus is present in the infected tissue in such a low concentration that it has so far been impossible to obtain a complement-fixing antigen from them. In others it has proved difficult to obtain antigen suspensions that are devoid of significant anticomplementary activity. This drawback is particularly serious in cases in which the concentration of the virus in the tissues is low and the corresponding antigen relatively weak in complement-fixing ability. Under these conditions any anticomplementary activity renders the interpretation of the test difficult at best, and special technics have been evolved to surmount this difficulty.

Again, since the source of antigen is infected tissue or fluid, it is necessary to include in each test an additional control consisting of normal tissue or fluid prepared in exactly the same way to rule out misleading nonspecific reactions. Parenthetically, it should be pointed out that in the identification of an unknown virus by serologic means a similar control must be included — that is, if the immune serum was obtained from a rabbit, the virus agent must be tested against normal rabbit serum as well.

Agglutination and flocculation tests. Diagnostic tests employed in agglutination or flocculation technics are little used in the study of virus diseases with the exception of smallpox. During the course of this disease the patient develops antibodies that agglutinate suspensions of vaccinial elementary bodies.[37] Conversely, if a suspension of ground-up variolous crusts is mixed with antivaccinial rabbit serum, flocculation occurs and thus furnishes a practical method for the diagnosis of doubtful cases of smallpox.[38–40]

Hemagglutinin-inhibition tests. The virus agents of certain diseases, notably influenza,[41] mumps[22] and vaccinia,[42] have the property of agglutinating the red cells of certain avian and mammalian species to a varying degree. Fowl erythrocytes are most widely used, but in some cases human Type "O" cells or guinea-pig erythrocytes may be substituted. This phenomenon furnishes a convenient method of titrating virus activity, and as such is widely employed in many laboratories, particularly in those in which influenza studies are being carried out. Analogous to what happens in neutralizing or complement-fixing antibodies, the patient with influenza develops antibodies that inhibit the ability of the virus to agglutinate fowl or human erythrocytes. After the hemagglutinating activity of the virus agent has been determined, four minimal

agglutinating doses of the virus are added to increasing dilutions of the serum to be tested, and fowl or other mammalian erythrocytes are added. In this manner the ability of two or more specimens of serum from a suspected case to inhibit hemagglutination may be compared. A significant rise in titer permits one to make a diagnosis of the disease. Here again the finding of inhibitory antibodies in a single specimen of serum gives only the limited information that at some time in the past the patient has been in contact with specific virus, either through clinical or subclinical illness or through vaccination. The finding of a high titer of antibodies against influenza A or B in a group of 10 to 20 persons recently recovered from an epidemic respiratory disease, however, strongly suggests that the outbreak was due to the specific virus. Since the test will distinguish between influenza A and B, it is a valuable tool in the hands of the epidemiologist for identifying the causative agent of an outbreak of influenza.

As has been pointed out, the mumps virus and the vaccinia virus also possess the ability to agglutinate erythrocytes of various mammalian species, and it is possible that the hemagglutination-inhibition reaction will be developed as a helpful diagnostic tool for some cases of the former disease at least.

Pathology

Most virus agents show predilections for certain types of tissue, and by virtue of these special affinities they are frequently classified as neurotropic (rabies, lymphocytic choriomeningitis, poliomyelitis and the various encephalitides), dermotropic (herpes, variola, varicella, vaccinia and the other human and animal poxes), viscerotropic (yellow fever and mumps) or respiratory (influenza A and B and psittacosis). It is not surprising, therefore, that some virus agents may be identified by the typical pathologic lesions that they produce. Furthermore, certain viruses cause characteristic intranuclear or intracytoplasmic structures, called "inclusion bodies," within the cells that they parasitize, which are quite pathognomonic of the causative agent. The best known of these is the intracytoplasmic Negri body,[42] which is pathognomonic for rabies, but many other virus agents produce analogous bodies, such as the Guarnieri bodies[44] of vaccinia and variola (intracytoplasmic) and the intranuclear inclusion bodies characterizing the lesions of herpes febrilis,[45] herpes zoster[45] and varicella.[46] These inclusion bodies have their chief diagnostic value in the examination of material obtained at autopsy — for example, the finding of typical Negri bodies in the nerve cells of the hippocampus of man or dog is pathognomonic of rabies and, in a dog that has bitten a human being, is a definite indication for the administration of rabies vaccine to the latter.

Skin Tests

In at least four diseases of viral origin (lymphogranuloma venereum, mumps, vaccinia and influenza), it is possible to demonstrate the development of altered skin sensitivity to the virus agent — or some product of it. In the first disease the Frei test consists in the injection of pus from a bubo,[47] of infected mouse-brain suspension[48] or of yolk-sac material from infected chick embryo.[31] A positive test is evidenced by the development of an infiltrated inflammatory area with a small, well defined papula. In the Enders test for mumps the material used is a suspension of infected monkey parotid gland[22] or infected material from the chick embryo.[49, 50] As in lymphogranuloma inguinale the reaction reaches its height in forty-eight hours; under proper conditions it fails to show definite necrosis. Since a positive reaction may be due to past as well as present infection, a diagnosis of existing clinical disease cannot be made on the results of the test alone but must be interpreted in the light of the clinical picture. The skin-test materials employed in both these diseases are antigenic and stimulate the production of antibodies that may confuse the serologic picture by causing falsely positive reactions. Hence it is important to complete the serologic diagnostic tests before the patient is tested for dermal hypersensitivity.

It has been shown that infection with influenza A or B viruses results in the development of dermal hypersensitivity to the specific virus or some product of it.[51] As yet no practical use has been made of this test for routine diagnostic work. The so-called "immune reaction" to vaccination with cowpox virus,[52] which occurs in persons who have suffered from smallpox or who have previously been vaccinated, is another example of dermal allergy resulting from infection with a virus agent.

Collection of Material

A large number of specimens received by any laboratory doing diagnostic work are apt to be unsatisfactory for testing for the possible presence of viruses because of the failure to realize that these agents are delicate organisms that quickly die out except under special conditions. Similarly, many serologic specimens sent in arrive contaminated or hemolyzed, or both, their value being thereby appreciably decreased. The proper collection and shipping of these materials is essential. An appreciation of some of the more important of these points will permit the laboratory to render far more assistance to the physician.

Specimens for the Isolation of Virus Agent

These usually consist of blood, spinal fluid, pharyngeal or nasopharyngeal washings or tissue. Unless the specimens can be brought to the laboratory within a matter of minutes special treat-

ment to ensure the viability of the suspected virus agent is necessary. Freezing is the easiest and generally the most practicable method of preserving these agents, and the use of dry ice (solid carbon dioxide) facilitates this process. Blood in amounts of at least 10 to 15 cc. should be withdrawn with a dry sterile syringe and placed in the refrigerator. As soon as clotting has taken place the specimen should be centrifuged, and the serum withdrawn aseptically and stored in sterile pyrex Wassermann tubes or vaccine bottles. The pyrex tubes should be sealed with an oxygen flame, and the bottles with rubber stoppers and pull-on aprons. Spinal fluid should be obtained with sterile precautions and similarly stored. For throat and nasopharyngeal washings it is customary to use nutrient broth or buffered isotonic sodium chloride, sometimes fortified with 10 per cent normal rabbit serum. These washings may be spun slowly for a few minutes to throw down the grosser particles, and the supernatant drawn off and stored in proper tubes or vials.

Freezing the contents of the bottles and vials is accomplished by immersing the tubes or vials in a mixture of alcohol and dry ice and rotating them during freezing to reduce the chance of breaking due to expansion of the fluid. The tubes or vials should be carefully wrapped in cotton wool and paper to prevent breakage and packed in a vacuum bottle surrounded by pieces of dry ice. If the tubes or vials are not properly wrapped they are apt to be cracked in transit. Enough dry ice must be put in to keep the material frozen during the period of shipping to the laboratory, which should be reduced to a minimum.

Samples of tissue submitted for virus studies should preferably be placed in wide-mouthed sterile bottles sealed with a rubber stopper held in place by adhesive tape. The material may then be frozen as outlined above and shipped to the laboratory packed in dry ice. Tight stoppering of the tube or bottle is necessary to prevent the ingress of carbon dioxide, since the acid reaction produced by this gas may inactivate the virus agent. If this is not possible, the second method of choice is to ship the tissue blocks in sterile containers filled with sterile 50 per cent neutral glycerin to a level where the tissue is completely submerged. If the possibility of delay in shipping the specimen exists and it is not feasible to maintain the supply of dry ice in the vacuum bottle the second method is the one of choice.

Although it is possible to preserve virus agents in the dried state by the use of the lyophilization apparatus, such a procedure is rarely necessary or practical under the conditions governing the clinician.

Specimens for Serologic Tests

Specimens of blood for neutralization, complement-fixation, flocculation and hemagglutination-inhibition tests should not be frozen. A generous sample of blood (at least 15 cc., if possible), should be withdrawn under sterile conditions, a dry syringe being used. After clotting and centrifugation the serum should be removed aseptically and shipped in a suitable sterile rubber-stoppered tube. It is best to store the specimen from the acute phase in the refrigerator at 4°C. until the sample from the convalescent phase is obtained. Both tubes should then be shipped together. Although refrigeration in transit is not necessary the specimens should be protected if possible from high temperatures and should be shipped to the laboratory by the most expeditious route.

All specimens should be suitably labeled so as to ensure their proper identification, and a brief abstract of the clinical history should accompany them.

References

1. Burnet, F. M. *Virus as Organism: Evolutionary and ecological aspects of some human virus diseases.* 134 pp. Cambridge, Mass.: Harvard University Press, 1945. P. 20.
2. Trask, J. D., Paul, J. R., and Vignec, A. J. Poliomyelitic virus in human stools. *J. Exper. Med.* **71**:751-763, 1940.
3. Kalter, S. S., Mordaunt, V. D., and Chapman, O. D. Isolation of *Escherichia coli* phage by means of cationic detergents. *J. Bacteriol.* **52**:237-240, 1946.
4. Personnel of U. S. Naval Laboratory Research Unit No. 1. Method for removal of bacterial contamination from suspensions of influenza virus. *Science* **96**:543, 1942.
5. Hirst, G. K. Direct isolation of human influenza virus in chick embryos. *Proc. Soc. Exper. Biol. & Med.* **58**:155-157, 1945.
6. Beveridge, W. I. B., Lind, P. E., and Anderson, S. G. Mumps. I. Isolation and cultivation of virus in chick embryo. *Australian J. Exper. Biol. & Med.* **24**:15-19, 1946.
7. Rivers, T. M. Virus diseases of nervous system. *J. A. M. A.* **132**: 427-430, 1946.
8. Armstrong, C., and Wooley, J. G. Studies on origin of newly discovered virus which causes lymphocytic choriomeningitis in experimental animals. *Pub. Health Rep.* **50**:537-541, 1935.
9. Wooley, J. G., and Armstrong, C. Distribution of immunity against encephalitis virus of St. Louis type in United States as determined by serum-protection test in white mice. *Pub. Health Rep.* **49**: 1495-1505, 1934.
10. Webster, L. T., Fite, G. L., and Clow, A. D., and Muench, H. Experimental studies on encephalitis. IV. Specific inactivation of virus by sera from persons exposed to encephalitis, St. Louis type, 1933, with note on correlation of results of mouse tests of sera. *J. Exper. Med.* **62**:827-847, 1935.
11. Webster, L. T. Japanese B encephalitis virus: its differentiation from St. Louis encephalitis virus and relationship to louping ill virus. *J. Exper. Med.* **67**:609-618, 1938.
12. Olitsky, P. K., and Harford, C. G. Intraperitoneal and intracerebral routes in serum protection tests with virus of equine encephalomyelitis. A. Comparison of two routes in protection tests. *J. Exper Med.* **68**:173-189, 1938.
13. Aycock, W. L., and Kramer, S. D. Immunity to poliomyelitis in normal individuals in urban and rural communities as indicated by neutralization test. *J. Prev. Med.* **4**:189-200, 1930.
14. Kolmer, J. A., and Rule, A. M. Tests for immunity to acute anterior poliomyelitis. I. Technique and status of monkey serum neutralization or antiviral test. *J. Immunol.* **29**:175-189, 1935.
15. Theiler, M. Studies on action of yellow fever in mice. *Ann. Trop. Med.* **24**:249-272, 1930.
16. Sawyer, W. A., and Lloyd, W. Use of mice in tests of immunity against yellow fever. *J. Exper. Med.* **54**:533-555, 1931.
17. Andrewes, C. H., Laidlaw, P. P., and Smith, W. Influenza: observations on recovery of virus from man and on antibody content of human sera. *Brit. J. Exper. Path.* **16**:566-582, 1935.
18. Keogh, E. V. Titration of vaccinia virus on chorioallantoic membrane of chick embryo and its application to immunological studies of neuro-vaccinia. *J. Path. & Bact.* **43**:441-454, 1936.
19. Burnet, F. M., and Lush, D. Inactivation of herpes virus by immune sera: experiments using chorio-allantoic membrane technique. *J. Path. & Bact.* **48**:275-286, 1939.
20. Shaffer, M. F., and Enders, J. F. Quantitative studies on infectivity of virus of herpes simplex for chorio-allantoic membrane of chick embryo, together with observations on inactivation of virus by its specific antiserum. *J. Immunol.* **37**:383-411, 1939.
21. Enders, J. F., Kane, L. W., Cohen, S., and Levens, J. H. Immunity in mumps. I. Experiments with monkeys (*Macacus mulatta*). Development of complement-fixing antibody following infection and experiments on immunization by means of inactivated virus and convalescent human serum. *J. Exper. Med.* **81**:93-117, 1945.
22. Enders, J. F., Cohen, S., and Kane, L. W. Immunity in mumps. II. Development of complement-fixing antibody and dermal hypersensitivity in human beings following mumps. *J. Exper. Med.* **81**:119-135, 1945.

23. Kane, L. W., and Enders, J. F. Immunity in mumps. III. Complement fixation test as aid in diagnosis of mumps meningoencephalitis. *J. Exper. Med.* **81**:137-150, 1945.
24. Howitt, B. F. Complement fixation reaction in experimental equine encephalomyelitis, lymphocytic choriomeningitis and St. Louis type of encephalitis. *J. Immunol.* **33**:235-250, 1937.
25. Casals, J., and Palacios, R. Complement fixation test in diagnosis of virus infections of central nervous system. *J. Exper. Med.* **74**: 409-426, 1941.
26. Smadel, J. E., Baird, R. D., and Wall, M. J. Soluble antigen of lymphocytic choriomeningitis. I. Separation of soluble antigen from virus. *J. Exper. Med.* **70**:53-66, 1939.
27. Havens, W. P., Watson, D. W., Green, R. H., Lavin, I., and Smadel, J. E. Complement fixation with neurotropic viruses. *J. Exper. Med.* **77**:139-153, 1943.
28. Fairbrother, R. W., and Hoyle, L. Observations on aetiology of influenza. *J. Path. & Bact.* **44**:213-223, 1937.
29. Francis, T., Magill, T. P., Rickard, E. R., and Beck, M. D. Etiological and serological studies in epidemic influenza. *Am. J. Pub. Health* **27**:1141-1160, 1937.
30. Francis, T., Jr. Differentiation of influenza A and influenza B by complement fixation-reaction. *Proc. Soc. Exper. Biol. & Med.* **45**: 861-863, 1941.
31. Shaffer, M. F., Rake, G., and Grace, Q. W. Yolk sac antigens in diagnosis and epidemiology of lymphogranuloma venereum. *Am. J. Syph., Gonor. & Ven. Dis.* **26**:271-281, 1942.
32. Smadel, J. E., Wertman, K., and Regan, R. L. Yolk sac complement fixation antigen for use in psittacosis-lymphogranuloma venereum group of diseases. *Proc. Soc. Exper. Biol. & Med.* **54**:70-74, 1943.
33. Levens, J. H., and Enders, J. F. Hemagglutinative properties of amniotic fluid from embryonated eggs infected with mumps virus. *Science* **102**:117-120, 1945.
34. Enders, J. F. Chemical, clinical and immunological studies on products of human plasma fractionation. X. Concentrations of certain antibodies in globulin fractions derived from human blood plasma. *J. Clin. Investigation* **23**:510-530, 1944.
35. Hoyle, L., and Fairbrother, R. W. Antigenic structure of influenza viruses: preparation of elementary body suspensions and nature of complement-fixing antigen. *J. Hyg.* **37**:512-520, 1937.
36. Craigie, J., and Wishart, F. O. Complement-fixation reaction with elementary bodies of vaccinia and specific precipitable substance of vaccinia. *Tr. Roy. Soc. Canada* (Third Series) **28** (Sec. V): 91-96, 1934.
37. Amies, C. R. Agglutination reaction in variola. *Lancet* **2**:558-560, 1932.
38. Gordon, M. H. *Studies of the Viruses of Vaccinia and Variola.* Medical Research Council, Special Report Series, No. 98. 135 pp. London: His Majesty's Stationery Office, 1925.
39. Burgess, W. L., Craigie, J., and Tulloch, W. J. *Diagnostic Value of the "Vaccinia-Variola" Flocculation Test.* Medical Research Council, Special Report Series, No. 143. 43 pp. London: His Majesty's Stationery Office, 1929.
40. Craigie, J., and Tulloch, W. J. *Further Investigations on the Variola-Vaccinia Flocculation Reaction.* Medical Research Council, Special Report Series, No. 156. 129 pp. London: His Majesty's Stationery Office, 1931.
41. Hirst, G. K. Quantitative determination of influenza virus and antibodies by means of red cell agglutination. *J. Exper. Med.* **75**:49-64, 1942.
42. Nagler, F. P. O. Application of Hirst's phenomenon to titration of vaccinia virus and vaccinia immune serum. *M. J. Australia* **1**: 281-283, 1942.
43. Negri, A. Beitrag zum Studium der Aetiologie der Tollwuth. *Ztschr. f. Hyg. u. Infectionskrankh.* **43**:507-527, 1903.
44. Guarnieri, G. Über die Parasiten der Variola und der Vaccine. *Centralbl. f. Bakt.* **16**:299, 1894.
45. Lipschutz, B. Untersuchungen über die Aetiologie der Krankheiten der Herpesgruppe (Herpes zoster, Herpes genitalis, Herpes febrilis) *Arch. f. Dermat. u. Syph.* **136**:428-482, 1921.
46. Tyzzer, E. E. Histology of skin lesions in varicella. *Philippine J. Sc.* **1**:349-372, 1906.
47. Frei, W. Eine neue Hautreaktion von "Lymphogranuloma inguinale." *Klin. Wschr.* **4**:2148, 1925.
48. Grace, A. W., and Suskind, F. H. Lymphogranuloma inguinale. III. Use of lymphogranulomatous mouse brains for diagnosis. *Arch. Dermat. & Syph.* **34**:65-78, 1936.
49. Habel, K. Cultivation of mumps virus in developing chick embryo and its application to studies of immunity to mumps in man. *Pub. Health Rep.* **60**:201-212, 1945.
50. Enders, J. F., Kane, L. W., Maris, E. P., and Stokes, J., Jr. Immunity in mumps. V. Correlation of presence of dermal hypersensitivity and resistance to mumps. *J. Exper. Med.* **84**:341-364, 1946.
51. Beveridge, W. I. B., and Burnet, F. M. Cutaneous reactions to influenza viruses. *M. J. Australia* **1**:85-89, 1944.
52. Jenner, E. *An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow-Pox.* 75 pp. London: S. Low, 1798. P. 13.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33421

PRESENTATION OF CASE

First admission. A sixty-three-year-old typewriter mechanic entered the hospital complaining of shortness of breath.

He had been in good health until three years before admission, when he developed a cold with considerable cough productive of heavy brownish sputum. He was placed on digitalis and bed rest for eight weeks. He returned to work and had no further difficulty for two years except for shortness of breath on climbing stairs. During the year prior to entry he had several attacks of nocturnal dyspnea with cyanosis. There had been no pain in the chest or swelling of the ankles. A heart murmur had been discovered at the age of twenty years during an examination for life insurance. Twenty years later, the patient had a severe attack of arthritis involving the shoulders most severely. There had been no arthritis or rheumatism before or after this episode. At the age of forty-seven years an elevated blood pressure was noted for the first time.

Physical examination revealed a well developed and well nourished man in mild respiratory distress with rapid respirations. The fundi showed slight arteriovenous nicking. The heart was enlarged on percussion. The rhythm was grossly irregular. Basal systolic and diastolic murmurs were heard. A high-pitched to-and-fro sound was noted at the apex and over the aortic area. Crackling rales were present at both bases. The liver was palpable three fingerbreadths below the costal margin.

The temperature was 97°F., the pulse 72, and the blood pressure 170 systolic, 94 diastolic.

Examination of the blood revealed a hemoglobin of 12.2 gm. and a white-cell count of 11,300, with 83 per cent neutrophils. The nonprotein nitrogen was 29 mg. per 100 cc. The urine had a specific gravity of 1.019 and gave a + test for albumin and a 0 test for sugar.

X-ray examination of the chest showed the heart to be generally enlarged, measuring 18 cm. in total diameter (internal chest diameter, 31.2 cm.). A film taken in the right oblique position disclosed a localized enlargement of the left auricle and the left ventricle displacing the esophagus posteriorly. The hilar shadows were prominent, with increased

vascular shadows throughout both lung fields. A small quantity of fluid was thought to be present in the left pleural cavity. Under fluoroscopy it was noted that the ventricular pulsations were totally irregular in rate, rhythm and amplitude.

The patient was placed on a low-sodium diet and given digitalis, ammonium chloride and Mercupurin; he quickly improved except for intermittent Cheyne–Stokes respirations. By the time of discharge two weeks later he had lost 10 pounds, and the respiratory symptoms had subsided completely.

Final admission (six months later). At home the patient did well for three months on a low-sodium diet with ammonium chloride and digitalis. He then noted the onset of polyuria and polydipsia and lost 12 pounds over a three-week period despite an adequate intake. Examination of the urine revealed a brick-red sugar test. The blood sugar was 441 mg. per 100 cc. The patient was given 20 units of protamine-zinc insulin daily and was well controlled thereafter, with blue and occasional green tests. During the six weeks before admission the attacks of breathlessness returned. These were at first relieved by the administration of a mercurial diuretic. Finally, a dry, persistent cough and a return of Cheyne–Stokes respirations were noted. In addition, the patient complained of a plugged sensation in both ears and a feeling of fullness in the epigastrium.

On admission the patient was severely orthopneic. The neck veins were distended in the sitting position. The left border of cardiac dullness was 11 cm. from the midsternal line. The rhythm was absolutely irregular, with a rate of 90. Grade III aortic systolic and diastolic murmurs were heard, as well as a Grade II apical systolic murmur. An easily heard apical diastolic rumble was noted. Moist rales were present in both lung fields to the level of the scapula on the right and higher on the left. The liver edge was palpable and slightly tender three or four finger-breadths below the costal margin. There was minimal pitting edema of the ankles.

The temperature was 98.8°F., and the blood pressure 178 systolic, 100 diastolic.

Examination of the blood disclosed a hemoglobin of 11.4 gm. and a white-cell count of 12,400, with 84 per cent neutrophils. The fasting blood sugar was 84 mg., and the nonprotein nitrogen 45 mg. per 100 cc. The urine had a specific gravity of 1.018 and gave a ++ test for albumin and a 0 test for sugar. The sediment contained 1 red cell and 3 white cells per high-power field.

There was no appreciable change in the x-ray appearance of the chest since the previous examination.

The patient was given 0.2 mg. of Purodigin daily. On the day following admission 1 cc. of Mercuhydrin was given. The urinary output for the next twenty-four hours, however, was only 640 cc. The dyspnea continued. Mercuhydrin injection was repeated, with no diuretic response.

On the seventh hospital day the patient complained of a steady pain in the right lower quadrant with local tenderness. The liver was no more enlarged or tender than on admission. On the same day he was found to be more severely dyspneic, with respirations of 40 to 50 per minute. He was considerably improved with oxygen, morphine and aminophylline. Examination of the legs at that time was negative.

During the next few days the patient became extremely lethargic. The nonprotein nitrogen rose to 110 mg. per 100 cc. The urinary output varied between 500 and 1000 cc. daily. The breath became frankly uremic. The abdomen was distended, tympanitic and soft. Fluid intake was increased to 3030 cc. on the thirteenth hospital day, with an output of 1140 cc. Urinalysis showed specific gravities of 1.016 to 1.020, + to ++ tests for albumin and a 0 test for sugar. The sediment showed up to 5 red cells and 20 white cells per high-power field. Although the nonprotein nitrogen level dropped temporarily, the clinical appearance remained unchanged. On the fifteenth hospital day a leathery pleural friction rub was noted along the right heart border. During the following week the friction rub grew more widespread, being heard in the right anterior portion of the chest and in the axilla. There were flatness and diminished breath sounds in the right lower portion of the chest posteriorly. Occasionally small amounts of rusty sputum were raised. A chest film showed a small amount of fluid on the right, with areas of atelectasis in the right lower lobe decreasing the size. His condition grew gradually worse, and he expired on the twenty-sixth hospital day.

Differential Diagnosis

Dr. Conger Williams: This sixty-three-year-old man died a year and a half after the onset of the cardiac symptoms. He apparently died in cardiorenal failure and possibly with complications in addition to uremia, such as pulmonary infection or infarction and even renal infarction, but I think that it is important at this point to decide what was the underlying lesion in the heart.

First of all, I considered the possibility of rheumatic heart disease, in spite of the patient's age. It is not unusual for a man with rheumatic heart disease to survive to the age of sixty and beyond. We know that at twenty years of age he was turned down for life insurance because of the discovery of cardiac murmurs. This may have been significant; at least, it is suggestive. At the age of forty-seven there was some evidence of arthritis. The episode is not described in detail, but it may have represented an exacerbation of rheumatic fever. Another point in keeping with rheumatic heart disease is the description of the murmurs. I take it, from what I read of the murmurs, that the patient had aortic stenosis and regurgitation. But he might have had

mitral stenosis as well, although the diastolic rumble was not heard at the time of the first admission. This does not mean that it was not present. There may have been other factors, such as congestive heart failure, that made it difficult to hear the murmur at that time. Another finding that is at least consistent with mitral stenosis, although not diagnostic, is auricular fibrillation. With the onset of auricular fibrillation, the character of a mitral diastolic murmur will change, as a result of disappearance of the presystolic crescendo, leaving a mid-diastolic rumble, such as that described at the time of the second admission. A diastolic rumble, however, is also found in dilatation of the left ventricle without mitral stenosis. So far, I can see nothing that makes me rule out rheumatic heart disease with or without mitral stenosis to explain these findings.

Next, the possibility of syphilis must be considered. The murmur of syphilitic aortic regurgitation is often a to-and-fro murmur, with a fairly loud systolic component. But again, in the case under discussion, the diagnosis of syphilis can only be mentioned. We are given no information about the blood Wassermann or Hinton reaction, nor do we know anything about a past history of syphilis. Certainly, the description of the aortic murmurs is compatible with that of syphilitic aortitis. It is possible that this patient had a combination of syphilitic aortitis and something else. We know that he had hypertension, but I suspect that it played an unimportant role, at least in the heart disease.

Calcareous aortic stenosis is possible but is usually not associated with a diastolic blow. There is a school of thought that holds that calcareous aortic-valve disease is always on a rheumatic basis. That is not a point to be settled now.

Another possible cause of the presence of auricular fibrillation is chronic coronary heart disease. At this age the complication of auricular fibrillation without other heart disease to explain it is fairly common. I doubt that there was previous myocardial infarction, although there is no report of an electrocardiogram.

The possible causes of the terminal uremia should next be considered. Nephrosclerosis is perhaps the most probable cause in this situation. We should think of the possibility of mercurial poisoning because of the fact that the urinary output decreased after two mercurial diuretics. The toxicity of these compounds is increased in connection with a low urinary output following their administration. Although toxic mercurial nephrosis as a result of these diuretic compounds is rather unusual, there have been 2 reported cases. In one described here in conference a year and a half ago, there was a reasonable assumption that the final uremia was based on the use of mercurial diuretics.*

*Case records of the Massachusetts General Hospital (Case 31451). *New Eng. J. Med.* 233:567-570, 1945.

Another condition that seems to recur quite often in these conferences is that of primary glomerulonephritis, even in older patients. We have no right to make that diagnosis but only to suggest it.

Renal infarction in a patient with auricular fibrillation has already been mentioned. The patient in the case under discussion had uremia resulting from painless renal infarction without hematuria.

I should like to mention another possibility of renal disease — that is, intercapillary glomerulosclerosis. We know that the patient had diabetes, and we also know that he had had albumin in the urine for some time before death.

On the basis of these findings, therefore, I favor a diagnosis of rheumatic heart disease with aortic stenosis and regurgitation, mitral stenosis, auricular fibrillation, cardiac enlargement and congestive heart failure complicated by terminal uremia on the basis of nephrosclerosis and, possibly, a pulmonary infection or infarction in addition.

DR. EDWARD F. BLAND: Needless to say, this case was somewhat of a puzzle. To take the lesser problem first, the patient developed acute diabetes under our observation during the last two or three months. He had severe, extensive valvular heart disease. We thought that it was rheumatic with a hypertensive element, involving principally the aortic valve with stenosis and regurgitation, and like Dr. Williams, we were uncertain whether there was mitral disease in addition. Temporarily, he did well on a low-sodium regime. In fact, we were able to discontinue mercurial diuretics for some months prior to the terminal failure. Then, abruptly, he became worse and failed to respond to mercurial diuretics or anything else, with increasing evidence of uremia. We thought that there was infection or infarction somewhere in the body. We could not make a diagnosis of bacterial endocarditis. The cultures were negative, and it did not look like that. We were uncertain about possible rheumatic infection. He was slightly jaundiced, — that does not appear in the record, — but the van den Bergh reaction was 5 mg. per 100 cc., as I recall, which made us suspect more strongly infarction somewhere in the body. We wondered about terminal nephritis or terminal infection in the genitourinary tract, but we were unable to prove either. The patient failed to respond, and died in uremia.

DR. WILLIAMS: You did not think at the first admission that the to-and-fro sound described was a friction rub and that he had acute rheumatic myocarditis?

DR. BLAND: That was on the original admission. The terminal friction rub was of some interest. It was over the whole right lung, and of such intensity that it was easily palpable.

CLINICAL DIAGNOSES

Rheumatic and hypertensive heart disease, with aortic regurgitation.

Auricular fibrillation and congestive failure.
Pulmonary infarct.
Uremia.
Nephritis?

DR. WILLIAMS'S DIAGNOSES

Rheumatic heart disease, with aortic stenosis and regurgitation.
Mitral stenosis?
Cardiac enlargement.
Congestive heart failure.
Auricular fibrillation.
Nephrosclerosis.
Uremia.
Pulmonary infarction?

ANATOMICAL DIAGNOSES

Calcareous aortic stenosis.
Hypertrophy and dilatation of heart.
Thrombosis of right and left auricular appendages.
Pulmonary emboli and infarction.
Renal emboli, multiple, with infarction.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination showed massive renal infarcts. The right kidney, the side where the pain was, had multiple infarcts, which occupied two thirds of the cortex. The left kidney was enlarged and also showed a single infarct. The source of these emboli was, with little doubt, a thrombus in the left auricle. The auricular appendage was still massively filled with thrombus at the time of autopsy. There was also a large thrombus, and the right auricular appendage, which had been the source of pulmonary emboli, and the right lower lobe of the lung were almost completely involved by three separate infarcts that were nearly contiguous. Also, two infarcts were present in the left lower lobe. The valvular disease of the heart consisted of calcareous aortic stenosis with marked interadherence of the commissures. There is nothing that would allow one to be dogmatic regarding whether or not this developed on the basis of a congenital bicuspid valve, but the mitral valve was completely normal. There were no rheumatic stigmas in the myocardium. The friction rub was obviously due to pleuritis, secondary to the pulmonary infarction. There was a fibrinous exudate, 3 mm. thick, over the involved area.

DR. BLAND: Before we close, would you be willing to discuss the infrequency of hematuria in massive or extensive renal infarction?

DR. MALLORY: I was wondering if anyone would comment because this case and the other case discussed today* had massive renal infarction, but only occasional red cells were found in the urinary sediment.

DR. BLAND: We looked repeatedly for hematuria, but at no time were there more than a few red cells in the sediment.

*Case records of the Massachusetts General Hospital (Case 33311). *New Eng. J. Med.* 237:163-167, 1947.

CASE 33422

PRESENTATION OF CASE

A seven-year-old boy was admitted to the hospital with extreme dyspnea.

About five weeks prior to admission the child began to complain of dyspnea on exertion. Ten days later vomiting, diarrhea and pain in the right upper quadrant developed, and he began to have rapid, grunting respirations. He was admitted to another hospital, where examination revealed myocardial enlargement in all diameters, with a faint systolic murmur at the apex and an enlarged tender liver. The blood pressure was 80 systolic, 60 diastolic. During the hospital stay the temperature remained normal, and the sedimentation rate was not elevated. An electrocardiogram showed marked left-axis deviation, with a slightly prolonged PR interval. Digitalis was administered, with no appreciable effect. The patient was also given mercurial diuretics, with a good output following the first two doses, but no increase was subsequently noted. After about three weeks of hospitalization, with a steady downhill course, he was admitted to this hospital.

There was a history of partial deafness since birth, aggravated by an attack of whooping cough at the age of four years, and also of subsistence on a diet composed largely of "Coca-Cola," "soda" and pastry for several months.

Physical examination disclosed a poorly nourished, cyanotic boy, who was gasping for breath and partially disoriented. The cardiac impulse was in the sixth left interspace in the anterior axillary line. The heart sounds were of poor quality, and a gallop rhythm was present. A pericardial friction rub was heard at the apex. There were a few moist rales at both bases posteriorly, and a questionable pleural friction rub was heard. The liver edge was palpated 4 cm. below the right costal margin, and was tender.

The temperature was 95°F., the pulse 120, and the respirations 60. The blood pressure was unobtainable.

Examination of the blood revealed a red-cell count of 4,680,000 and a white-cell count of 4800, with 88 per cent neutrophils. The urine had a specific gravity of 1.020 and contained a moderate trace of albumin, and many casts were observed in the sediment. An electrocardiogram showed a rate of 150, with a PR interval of 0.14 second and some evidence of intraventricular block.

Cedilanid (0.4 mg.) and fluids were administered intravenously. The patient followed a rapid downhill course and died about eight hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. GERTRUD E. REYERSBACH: This is a history of myocarditis and congestive failure, and the prob-

lem is to decide what type of myocardial disease this child had.

The most frequent cause of myocarditis in childhood is rheumatic fever. In most cases myocardial involvement in rheumatic fever is accompanied by fever. Severe myocardial disease without involvement of the endocardium, — that is, without valvular lesions, is rare. The patient is reported to have had a faint systolic apical murmur. This description does not fit too well with valvular disease, but the murmur may have been due to cardiac dilatation and a relative mitral insufficiency.

The prolonged PR interval — we do not know how much prolonged — is consistent not only with a diagnosis of rheumatic carditis but also with some other forms of carditis. We do not know whether the electrocardiogram was taken before digitalis was administered. A normal sedimentation rate in the presence of congestive failure is frequent in rheumatic carditis. Failure to respond to digitalis is not rare, but in this case it may have been due to the fact that inadequate doses of digitalis were administered.

The absence of any other signs of rheumatic fever, such as joint pains, nodules, rashes and epistaxis, makes the diagnosis of rheumatic myocarditis unlikely.

We then come to a second group of diseases that may cause myocarditis in this age group — namely, infection. There is no indication that this boy had such a disease as typhoid fever or that he had a septicemia. Diphtheria is known to cause severe myocarditis. No mention is made of a sore throat or a skin lesion that might have been of diphtheritic origin. A prolonged PR interval, intraventricular block and low blood pressure are often seen in diphtheritic myocarditis, but cardiac dilatation is comparatively rare. Furthermore, one would have expected the boy to succumb earlier had he had diphtheritic myocarditis.

Nothing in the history suggests hyperthyroidism or hypothyroidism, nor is there any mention of the ingestion of such poisons as phosphorus, arsenic and chloroform.

We know that myocarditis occurs in acute hemorrhagic nephritis. I think that we can safely discard this diagnosis without further discussion. Also, the diagnosis of chronic nephritis with cardiac failure can be eliminated. True, a urine examination showed albumin and casts, but these findings are not uncommon in congestive failure. I doubt that they were due to mercury poisoning.

It is said that the patient had subsisted on a diet comprised largely of Coca-Cola, soda and pastry for a few months before becoming sick. This indicates that the diet was poor in thiamine. Did the patient have beriberi? We are not told whether any signs of polyneuritis were found or whether the deep reflexes were diminished. A serum protein determination is not recorded. In beriberi, the blood pressure is usually low, as in this patient. The heart is greatly enlarged, often generally, sometimes the right side more so than the left. The electrocardiogram usually shows low voltage of QRS segments and T waves. A diagnosis can only be made by clinical observation, careful appraisal of the diet and sometimes a clinical trial with thiamine.

Two rare congenital lesions that produce cardiac insufficiency are the cardiac form of glycogen disease and rhabdomyoma of the heart. In both diseases hypertrophic heart-muscle cells containing large vacuolated spaces filled with glycogen are found. Practically all reported cases of rhabdomyoma have been associated with tuberous sclerosis, of which this child showed no signs.

He may have had cardiac glycogen disease; we cannot make the diagnosis positively during life. I do believe that the large liver was not due to glycogen disease but to congestive failure.

Lastly, we come to the group of interstitial myocarditis described by Fiedler.[1] In these cases cardiac enlargement, often with no murmurs, and congestive failure are apparent clinically. These children are usually afebrile and do not respond well to digitalis or diuretics. The disease is more frequently found in smaller children but has been described in a child of the same age as this patient. The clinical picture and course fit well with this disease.

In making a diagnosis, I believe that we must consider seriously three possibilities: beriberi, glycogen disease and interstitial myocarditis. It is unlikely, however, that he had beriberi myocarditis. I am sure that he must have had thiamine before he went on this peculiar diet, and also I should think that he had received thiamine in some form in the other hospital. This type of myocarditis is more frequently seen in infants with a poor dietary history than in older children. I must therefore decide between glycogen disease and interstitial myocarditis, and I shall guess that he had interstitial myocarditis, congestive failure and terminal pericarditis.

Dr. Alfred Kranes: Do you think that the electrocardiographic findings are against interstitial myocarditis?

Dr. Reyersbach: A little.

Clinical Diagnosis

Myocarditis.

Dr. Reyersbach's Diagnoses

Interstitial myocarditis.
Congestive failure.
Terminal pericarditis.

Anatomical Diagnoses

(Beriberi heart disease, probable.)
Diffuse fibrosis of myocardium.
Hypertrophy and dilatation of heart.
Chronic passive congestion.

Pathological Discussion

Dr. Tracy B. Mallory: Post-mortem examination showed primarily a hypertrophied heart weighing 210 gm. All the chambers were dilated and moderately hypertrophied. The pericardium contained fluid but was clear, and there was no evidence of pericarditis. The valves were entirely normal. The ventricular endocardium seemed slightly thickened. The musculature was not grossly abnormal, but when the microscopical sections came through, they presented a very unusual and interesting appearance. In all of a number of blocks there was diffuse fibrosis, with a moderate degree of edema of the interstitial fibrous tissue. There was no inflammatory infiltration, and there were no areas of necrosis or destruction of the cardiac muscle cells. These cells looked hypertrophied, as one would expect from the increased weight of the heart, and showed mild degenerative changes in which the muscle fibers were widely separated from one another by a homogeneous, slightly hyaline material, which I could not identify. A few cells showed hydropic vacuoles. There was no evidence of glycogen storage.

We are therefore presented with a diffuse fibrosis of the myocardium without evidence of present or past destruction of muscle cells or any traces of inflammation. Most types of myocarditis are associated with extensive destruction of muscle cells — for example, that seen in diphtheria. It is conceivable that an interstitial myocarditis such as is seen following sulfadiazine therapy or in typhus fever can result in fibrosis somewhat similar to what was observed in this case, but I would expect it to be focal rather than diffuse and there is not the least reason for suspecting such etiologic agents in this patient. On the other hand, this appearance has frequently been described in beriberi.[2–4] Although the histologic picture was not specific, the findings were compatible, and that is my first choice of diagnosis. We found nothing else in the rest of the body that was of any significance, except evidence of congestion and cardiac failure.

Dr. Allan M. Butler: In pediatrics we are often puzzled regarding why we do not see more thiamine deficiency because our infants exist on a diet that is very low in thiamine and often have severe bouts of nutritional disturbance. The diet is sometimes high in sugar, and yet we hardly ever see any objective evidence of thiamine deficiency.

Dr. Mallory: In this part of the world almost the only cases of frank beriberi heart disease are seen in chronic alcoholics.

Dr. Sedgwick Mead: Were there any changes in the peripheral nervous system?

Dr. Mallory: Unfortunately, they were not studied. There was no clinical evidence of neuritis, however.

References

1. Fiedler, A. Über akute interstitielle Myokarditis. *Centralbl. f. inn. Med.* **21**:212, 1900.
2. Saphir, O. Myocarditis: general review, with analysis of two hundred and forty cases. *Arch. Path.* **32**:1000-1051, 1941, and **33**:88-137, 1942.
3. Weiss, S., and Wilkins, R. W. Myocardial abscess with perforation of heart. *Am. J. M. Sc.* **194**:199-205, 1937.
4. Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S. Occidental beriberi heart disease. *J. A. M. A.* **131**:717-726, 1946.

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NEW ENGLAND POSTGRADUATE ASSEMBLY

THE sixth New England Postgraduate Assembly, the program of which appears elsewhere in this issue of the *Journal*, will be held at the Copley Plaza Hotel in Boston on October 29 and 30, with clinics at various hospitals in Greater Boston on the morning of October 31.

As in previous years, recognized leaders in the medical profession will present a series of lectures on subjects of general and special interest. The half day of clinics should enhance the appeal of the Assembly to practicing physicians. The technical exhibit by commercial firms will also provide an opportunity to become acquainted with the latest improvements in diagnostic aids and therapeutic agents.

From its inception, the Assembly has represented a co-operative effort on the part of the New England medical societies to present information on new and significant subjects in medicine and surgery. The Program Committee deserves praise for the selection of topics, which continues the high standard set in former meetings of the Assembly.

Attendance is expected to match that of previous years. The Assembly has become deservedly popular among physicians in New England as a valuable means of postgraduate education that affords an excellent opportunity of keeping up with advances in medicine and surgery. Those who attend the sessions and the clinics will be richly rewarded in knowledge and inspiration.

QUANTITY VERSUS QUALITY

MUCH of the thought concerning the distribution of medical care is based on the assumption that there is a store of unused potential medical care that should be properly distributed. We have sowed, harvested and gleaned our learning over the years. Now we are garnering it; let us open up the bins and release it to a long-starved public!

This idea suffers on closer inspection. Medical care consists of knowledge, applied by men to patients. This knowledge is the working capital of medicine, built up through centuries of experience and decades of research. We often proudly refer to modern medical knowledge as of "huge extent" or "staggering proportions," and relative to the accumulated facts of a century ago, this is true. Yet in any given area, knowledge is not so massive that it cannot be encompassed by the human intellect. Knowledge simplifies as it progresses, and multiple ill understood theories are swept away by the strong currents of new basic facts. Each significant advance in medicine renders obsolete a multitude of former writings or practices. There is nothing overpowering in the amount of our present knowledge, but the application of this knowledge to sick human beings is a complex and difficult affair that requires the use of the second medical resource, men. Without men who can apply it properly, medical knowledge is sterile. Unfortunately, an M.D. degree confers neither wisdom nor honesty on the recipient;

wisdom in its broader sense includes not only factual knowledge but also the ability to apply knowledge with judgment and mercy. Honesty is the *sine qua non* of medicine, without which medical practice degenerates into the collection of the fee without the contribution of commensurate benefit.

The question at hand is, Do we have any reservoir of men to apply our knowledge, any reservoir that is not drained, any potential that is not kinetic? Do we have any group of competent men whose present time-budget is ready for the expanded services of a legislative medical plan? A moment's consideration will reveal that we do not have such an unexpended surplus; indeed, we are operating with a deficit.

For all their effectiveness, modern medical technics are dangerous and medical knowledge is of little avail unless applied by men of wisdom and integrity. Modern tools enforce on us the necessity of becoming better craftsmen. When medical care was simple and ineffective it was also harmless, and the fine exercise of judgment required of the present-day physician, working with his sharp and penetrating weapons, was less frequently required. Yet the raw material from which physicians are fashioned has not changed since the day of Currier and Ives.

Recognition of the fact that the American medical profession is not perfect constitutes an unpopular viewpoint in this day of propaganda and institutional advertising; even the pharmaceutical industry seems to be in league to inflate our ego and whitewash our shortcomings. The prescient, sentient and omniscient doctor-scientist of the motion pictures and advertisements has become a fixture in the public mind and therefore in ours. Unfortunately, however, the profession does leave much to be desired; this is no disgrace, for any group of 160,000 men is too large to be called "select." The members of the medical profession possess all the virtues and all the faults of any large cross section of population. In addition to the wise and honest doctor-scientists, we have our full share of loud-mouthed snap diagnosticians; and researchers who are long on theory but short on judgment are as numerous as surgeons whose concern for the patient fades if convalescence is stormy.

These facts and this deficit of quality are disturbing only if we set out to distribute our allegedly undistributed medical care by legislative extension of medical services. In creating a broad national medical-care plan it should be recalled that the harm done by poorly qualified men becomes multiplied as the square of the number of patients they treat. There are all too few physicians who exemplify the best in the profession, and they are already overburdened.

How can this deficit be met? Is there any way of multiplying the good medical care dispensed by one person? In a limited sense, yes. One occasionally encounters that happy circumstance in which an older man surrounds himself with a group of devoted and effective residents or associates in a hospital or clinic and thus extends his reactive interface with the public. But this is a rare phenomenon. More frequently the able, older man becomes increasingly absorbed in administrative or other noneffective duties that enhance his national reputation but limit rather than extend his contact with the public. This type of work should be delegated to personnel trained for that purpose, not to the best clinicians and investigators.

Is there any way of increasing the total number of effectives? Better recruiting should be the answer. The admission committees of medical schools must raise their standards by every honest means. The interest and enthusiasm of the most capable undergraduates in the colleges must be aroused. The breed must be improved, even if it requires artificial insemination!

Until we have succeeded, let us not try to dispense to the public more medical care than we possess. We must meet out present deficit of quality before incurring any more obligations for quantity. One may raise the objection that the public will not wait — that labor unions or insurance groups will insist on the extension of medical care. Let them light the fire; they will be badly burned and learn their lesson. Some well intentioned and well financed group will establish a medical-care plan and, by chance or ignorance, will place it under the direction of poorly qualified physicians. The patients will be cared for by men with "pet theories," which were formerly inflicted on relatively small

groups of private patients, or by surgeons long on speed and short on incisions. But these patients will not drift off into the happy limbo of another man's practice. They have made their prepayments over the years and they will return for amends; the bad news will gather like flies around offal on a hot summer day. The backers of this scheme will come to realize that, although their expenses have been met, they are operating under a deficit — a type of deficit peculiar to medical undertakings.

The definition and control of competence is the central problem of medicine today. It seems wiser to move toward the solution of this problem than to multiply the total number of doctor-patient contacts by legislation.

A FITTING MEMORIAL

THE published notice of the services for the late Dr. Robert N. Nye contained a request that flowers be omitted but that in their stead donations be sent to the Massachusetts Division of the American Cancer Society. The request met with a remarkable response. In scarcely more than two weeks over $1600 had been received, none of it obtained by solicitation.

There is a growing sentiment that this sum should be expanded into a real memorial fund, in view of the great interest that Dr. Nye had in the American Cancer Society, and the time and effort that he had given to it in addition to his editorial and other duties.

Any persons who are interested in adding to this fund should send their donations, in Dr. Nye's name, to the American Cancer Society (Massachusetts Division) Inc., 476 Boylston Street, Boston 16.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HAWKINS — Henry Hawkins, M.D., of Belmont, died on September 4. He was in his seventy-fifth year.

Dr. Hawkins received his degree from University of Pennsylvania School of Medicine in 1902. He was ophthalmologist at the Perkins Institute for the Blind and the School for Crippled Children. He was on the staffs of the Boston City, Cambridge City and Cambridge Emergency hospitals and was a consulting surgeon to the Massachusetts General Hospital. He was a member of the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow and two sisters survive.

LUCAS — Julian D. Lucas, M.D., of Brookline, died on June 3. He was in his seventieth year.

Dr. Lucas received his degree from Tufts College Medical School in 1902. He was a former member of the Massachusetts Medical Society.

MURPHY — Harold A. Murphy, M.D., of Jamaica Plain, died on September 23. He was in his fifty-sixth year.

Dr. Murphy received his degree from Tufts College Medical School in 1915.

His widow, a son, two brothers and a sister survive.

APPLICANTS FOR FELLOWSHIP

The following three names were omitted from the list of applicants published in the *Journal* of October 9.

ESSEX NORTH DISTRICT

WEINSTEIN, MAX I., 220 Walnut Street, Lawrence. Middlesex University School of Medicine, 1936. Sponsor: N. F. DeCesare, 57 Jackson Street, Lawrence.

Harold R. Kurth, *Secretary*
57 Jackson Street, Lawrence

MIDDLESEX NORTH DISTRICT

PELOQUIN, LAVAL U., 834 Stevens Street, Lowell. Georgetown University School of Medicine.

Brendan D. Leahey, *Secretary*
9 Central Street, Lowell

MIDDLESEX SOUTH DISTRICT

PAGEL, MAX MANFRIED, 21 Clark Street, Newton Centre. University of Breslau, 1920. Sponsor: B. P. Colcock, 78 Hull Street, Newtonville.

Alexander A. Levi, *Secretary*
481 Beacon Street, Boston

A HUNDRED YEARS AGO

We have ever found it difficult to impress upon females the importance and absolute necessity of remaining for a sufficient length of time after confinement in a horizontal position, and keeping perfectly quiet. We are satisfied that the practise of getting out of bed too soon after confinement is very general in our community and hence it is that such a very large proportion of our female population suffer with prolapsus and procidentia uteri. Sometimes this is attributable to the want of proper precaution on the part of medical advisers, but more frequently it is owing to the folly of patients themselves. On the third or fourth day after parturition, a patient who is "very smart," feels able to sit up in bed, or in an easy chair, and in spite of all that the physician can say, she will, in his absence, sit up for the purpose of changing her clothes, or get out of bed altogether, that it may be made up, and not infrequently walk across the floor, by way of testing her strength. A moment's reflection must convince any one of the impropriety of such conduct. We are satisfied that if due attention were paid to the proper "getting up" after confinement, we would not see so many young and lovely wives, pale and anaemic, and unable to take the least exercise, or even attend to their ordinary household affairs, without the greatest pain. — A quarterly

meeting of the Counsellors of the Massachusetts Medical Society was held at the Masonic Temple a few days ago. There have not been so many Counsellors together at an ordinary business meeting within the compass of our recollection. Everything passed satisfactorily until Dr. Childs of Pittsfield resolved that *Whereas*, The great object of medical association is the advancement of medical science, and the promotion of harmony and good feeling in the profession, thereby contributing to the best interests of society, and *Whereas* the present organization of the Massachusetts Medical Society does not fully meet these important objects, therefore, *Resolved*, that a change in the organization of the Massachusetts Medical Society is in our opinion deemed both wise and expedient, and that the change consist in making the basis of the State Society, local or county associations. — The whole number of cases treated by the Physicians of the Boston Dispensary during the year ending Sept. 30, was 3290. The number of "Bostonians" in this list is stated in the Abstract of Reports as 163; other Americans, 458; Hibernico-Americans, 657; Irish, 1874. Only 150 of the patients are reported as intemperate. — A great variety of beautiful dental work was on exhibition at the late Quincy Hall fair. By ingenious clock machinery, artificial jaws of porcelain teeth were continually opening and closing, as spectators were passing along. — We are gratified to learn that a Professorship of Insanity has been established at one Medical School. The Willoughby University, Columbus, Ohio, has appointed Samuel M. Smith, M.D., Professor of Medical Jurisprudence and Insanity. We think there should be a distinct course of lectures on mental maladies, at every medical school. Dr. Smith has some practical knowledge of insanity, having been an Assistant Physician at the Ohio Lunatic Asylum for several years. — Died, in Pembroke, Mass., Dr. Anthony Collamore, a worthy physician and an honest man. The disease which occasioned this sad bereavement was dilatation of both auricles, and both ventricles of the heart, without hypertrophy. The pericardium was adherent to the heart, and also the diaphragm and mediastinum. Although confident that disease was praying upon his vitals, yet so slight was the uneasiness occasioned by the inflammation that he was scarce ever detained from attending to the duties of his laborious profession. He had been a practitioner of medicine in Pembroke nearly forty years. He was one of those old-fashioned physicians, who never blazon forth their cures as wonderful. Tender and sympathizing, he softened the pillow of the sick, and dropped a tear with relatives bereaved. Well can it be said, that those who knew him best, deplore him most. — Extracted from the *Boston Medical and Surgical Journal*, October, 1847.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LOCATION OF RESPIRATORS AND HOT PACK MACHINES IN MASSACHUSETTS*

City or Town	Location of Equipment	Respirators	Hot Pack Machines
	BARNSTABLE COUNTY		
Hyannis	Cape Cod Hospital	1	1
	BERKSHIRE COUNTY		
North Adams	North Adams Hospital	1	—
Pittsfield	House of Mercy Hospital	3	5
	BRISTOL COUNTY		
Attleboro	Sturdy Memorial Hospital	1	1
Fall River	Fall River General Hospital	1	2
	St. Anne's Hospital	1	—
	Truesdale Hospital	—	2
	Union Hospital	2	2
New Bedford	St. Luke's Hospital	2	1
Taunton	Morton Hospital	1	—
	ESSEX COUNTY		
Beverly	Beverly Hospital	2	—
Danvers	Hunt Memorial Hospital	1	—
Haverhill	Hale Hospital	1	—
Lawrence	Lawrence General Hospital	2	—
Lynn	Lynn Hospital	1	1
Newburyport	Anna Jaques Hospital	1	1
Peabody	J. B. Thomas Hospital	1	1
Salem	Salem Hospital	3	1
	FRANKLIN COUNTY		
Greenfield	Greenfield Isolation Hospital	1	1
	HAMPDEN COUNTY		
Holyoke	Holyoke Hospital	1	2
Springfield	Health Department Hospital	1	—
	HAMPSHIRE COUNTY		
Northampton	Cooley-Dickinson Hospital	1 adult 1 infant	1
Ware	Mary Lane Hospital	(1 resuscitator)	—
	MIDDLESEX COUNTY		
Cambridge	Cambridge City Hospital	1 adult 1 infant	—
Everett	Whidden Memorial Hospital	1	—
Framingham	Cushing General Hospital	1	—
	Framingham Union Hospital	1	—
Lowell	St. John's Hospital	—	3
Malden	Malden Hospital	1	—
Newton	Newton-Wellesley Hospital	—	1
	NORFOLK COUNTY		
Quincy	Quincy City Hospital	1 adult 1 infant	1
	PLYMOUTH COUNTY		
Brockton	Brockton Hospital	1	—
Middleboro	Lakeville State Sanatorium	2	3
	SUFFOLK COUNTY		
Boston	Beth Israel Hospital	2	—
	Boston City Hospital	6	3
	Carney Hospital	1	—
	Children's Hospital	3†	10
	Haynes Memorial Hospital	5	4
	Massachusetts General Hospital	6	3
	New England Baptist Hospital	1	—
	Peter Bent Brigham Hospital	3	1
	St. Elizabeth's Hospital	1	—
	St. Mary's Infant Asylum	1	—
	Veterans Administration Hospital (West Roxbury)	1	—
Chelsea	Chelsea Memorial Hospital	1	—
Revere	Revere General Hospital	1	—
Winthrop	Winthrop Community Hospital	1	—
	WORCESTER COUNTY		
Fitchburg	Burbank Hospital	1	2
Gardner	Henry Heywood Memorial Hospital	1	—
Worcester	Belmont Hospital	1	—
	Fairlawn Hospital	(1 resuscitator)	—
	Memorial Hospital	1	—
	Worcester City Hospital	3	—

*List compiled jointly by the Massachusetts Department of Public Health and the National Foundation for Infantile Paralysis.

†Also, 4-patient respirator room.

MISCELLANY

ALVARENGA PRIZE

The College of Physicians of Philadelphia awarded the Alvarenga Prize on July 14, 1947, for this year to Dr. Joseph Aronson, of the United States Bureau of Indian Affairs, in recognition of his studies on the evaluation of BCG vaccine in the control of tuberculosis.

The Alvarenga Prize was established by the will of Pedro Francisco daCosta Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians, to be awarded annually by the College of Physicians on each anniversary of the death of the testator, July 14, 1883, for outstanding work.

NOTES

The following Massachusetts physicians were recently appointed fellows in the American College of Surgeons: Thomas W. Botsford, Brookline; Weston T. Buddington, Boston; John H. Crandon, Boston; William H. Creamer, Fall River; William F. Croskery, Brookline; George F. Emerson, Boston; Francis J. Hanley, Brookline; Edward Harding, Brookline; J. Hartwell Harrison, Boston; Herbert E. Hedberg, Worcester; Donald Hight, Worcester; Stanley O. Hoerr, Boston; Elwood O. Horne, Worcester; Chester W. Howe, Framingham; George Kelemen, Boston; Benjamin deF. Lambert, Lowell; Henry C. Lawson, Fall River; Joseph P. Marnane, Gardner; John B. McKittrick, Boston; Carter R. Rowe, Boston; Morgan Sargent, Quincy; S. Peter Sarris, Lynn; John A. Seth, Boston; Artemas J. Stewart, Lowell; William W. Teahan, Holyoke; Robert S. Thomson, Roslindale; Howard M. Trafton, Dorchester; John B. Vernaglia, Medford; Joshua H. Weeks, New Bedford; Charles A. Wheeler, Leominster; and Hilary F. White, Fall River.

NORFOLK MEDICAL NEWS

The *Journal* welcomes the reappearance of the *Norfolk Medical News*, after an interval of two years during which it had suspended publication. Appearing first in 1940 and continuing in regular publication until 1945, the *News* appears now in its sixth volume. Distributed to the entire membership of the parent society, the *News*, offering the use of its pages as a general forum, is more than the journal of a single district.

CORRESPONDENCE

A PERTINENT SUGGESTION

To the Editor: Well trained physicians in the Commonwealth frequently see many patients who have been treated poorly — both professionally and financially — by other less well trained physicians, the majority of whom are graduates of medical schools unapproved by the Council on Medical Education and Hospitals of the American Medical Association. Furthermore, most of the physicians with inferior training take their patients to private hospitals not approved as Grade A by the Council on Medical Education and Hospitals. In these hospitals the standards are frequently poor, and surgical and medical care leave much to be desired.

The same physicians are not allowed to practice in first-rate hospitals. Moreover, until the recent institution by the Massachusetts Medical Society of refresher courses for physicians who are veterans, and for any other physicians who might wish to attend, little or no encouragement has been given physicians to improve their professional status and ability. If poor medicine, shabby ethics, and dangerously inadequate hospital care are to be prevented in the Commonwealth, all poorly trained physicians must be encouraged to improve their knowledge, and they must also be rewarded for such improvement. How can this be brought about?

It is my opinion that the Massachusetts Medical Society can do a great deal by offering prescribed courses to all physicians to be given throughout the year by the three leading medical schools in the Commonwealth. These courses should be for the express purpose of allowing those who pass the final examinations to qualify for admission to the courtesy staffs of Grade A hospitals.

Naturally, physicians passing the prescribed courses would also have to qualify morally and ethically. But that problem would rest with the Grade A hospitals that chose to admit to their staffs the physicians who had passed the required courses.

Now that recent legislation prohibits graduates of unapproved medical schools from obtaining licenses to practice medicine in Massachusetts, we have at last only to contend with all the physicians — graduates of the same unapproved schools — who already hold such licenses. Of course, unless they were strongly urged to do so, there would be many substandard physicians who would not take the required courses, and who therefore might never enjoy the benefits of caring for their patients in Grade A hospitals. There would be a great many other such physicians, however, now legally practicing medicine in the Commonwealth, who would jump at the chance to improve their knowledge and so to be accepted by approved medical institutions.

By the offering of such concrete encouragement and opportunity by the Massachusetts Medical Society many of these well meaning, but unhappily poorly trained physicians, would lose the "chip on their shoulders"; they would be *in* instead of *out* with the majority of their profession, and at the end of a few years the caliber of medical care in the Commonwealth would be greatly enhanced. The number of second-rate and third-rate private hospitals would be reduced materially.

It is hoped that the Society will work toward some such goal as I have outlined above.

J. Robert Lyman, M.D.

24 Forest Street
Wellesley Hills

BOOK REVIEW

Diseases of the Basal Ganglia and Subthalamic Nuclei. By D. Denny-Brown, M.D., C.H.C., Dr.Phil., F.R.C.P. 8°, cloth, 74 pp., with one colored plate. New York: Oxford University Press, 1946. $2.50. Reprinted from the Oxford Loose-Leaf Medicine.

This short monograph is issued as a reprint from *Oxford Loose-Leaf Medicine*, Volume VI, in a convenient form for those interested in the subject. The contents appear to be unchanged. There are a separate index and an extensive bibliography. One illustration in color is fairly satisfactory. The review, by a well known authority, is an excellent one, and all physicians seeking knowledge of the diseases of the basal ganglions are referred to this work. The chief clinical syndromes covered are paralysis agitans, postencephalitic Parkinsonism, hepatolenticular degeneration, dystonia, athetosis and Huntington's and other forms of adult chorea. Each disease is discussed from the point of view of definition, symptomatology, pathology and treatment. Although the article is brief and intended for reference by the internist or the general practitioner, the quality of the evaluations and the clearness of the presentation make this short monograph an outstanding contribution.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

La Douleur. By Dr. Paul Chauchard, directeur adjoint à l'École pratique des hautes Études. 128 pp., 12°, paper, with ten illustrations. Paris: Presses universitaires de France, 1947. Forms No. 252 of "Que sais-je?" Le point des connaissances actuelles.

This small popular work on pain is divided into three parts: physiology; pathology, including visceral, neuralgic and central-nervous-system pain; and treatment, including medical and surgical treatment and means for alleviating pain. The material is well organized, and the text well written. The catalogue of this popular series shows that the whole field of knowledge is well covered. The series should prove interesting to French-reading persons.

Annual Report of the Baruch Committee on Physical Medicine: For the period of April 1, 1945, to December 31, 1946. 8°, paper, 161 pp., with 35 illustrations. New York: The Committee, 1947. Free.

This is a comprehensive report of the activities carried on by thirteen medical schools supported by grants from the Baruch Committee. The total disbursement for the period under consideration was slightly over $107,369.

The Role of Hormones in Sterility. By Bent C. Böving, A.B. 4°, paper, 38 pp., with one plate. (The Schering award for 1946.) Bloomfield, New Jersey: Schering Corporation, Medical Department, 1947. Free.

This essay received first prize in a competition participated in by forty-eight contestants. Mr. Böving is now in the class of 1948 at the Jefferson Medical College. He discusses the various aspects of his subject, especially from the viewpoints of chemistry and physiology.

Copper and Health. Issued by the Copper and Brass Research Association. 8°, paper, 47 pp. New York: The Association, 1947. Free.

In this pamphlet the various aspects of copper in relation to health are discussed, including toxicity, value as a nutrient and use in cooking utensils, in water-supply systems and in ancient and modern medicine. Much of the information presented in the booklet was compiled by Dr. R. R. Sayers, director of the Bureau of Mines, Department of the Interior, when he was serving as chief of the Division of Industrial Hygiene, United States Public Health Service. He was assisted by Sara J. Davenport. The printing is well done with a good type on good paper. This small pamphlet should prove useful for reference purposes in all medical and general libraries.

Roentgen Interpretation. By George W. Holmes, M.D., member, Board of Consultation, Massachusetts General Hospital, and clinical professor of roentgenology, emeritus, Harvard Medical School; and Laurence L. Robbins, M.D., radiologist-in-chief, Massachusetts General Hospital, and associate in radiology, Harvard Medical School. Seventh edition, thoroughly revised. 8°, cloth, 398 pp., with 266 illustrations. Philadelphia: Lea and Febiger, 1947. $7.00.

This standard textbook has been thoroughly revised to include the advances in the subject since the publication of the previous edition, including particularly new material on diagnosis and treatment. The book is well published in every way. It should be in all medical libraries and in the libraries of physicians interested in radiologic diagnosis.

Recent Trends in Alcoholism and in Alcohol Consumption. By E. M. Jellinek, Sc.D., director, Section of Studies on Alcohol, Laboratory of Applied Physiology, Yale University. 4°, paper, 42 pp., with four figures and twenty-seven tables. New Haven: Hillhouse Press, 1947. 50 cents.

This is a statistical study of the apparent consumption of alcoholic beverages for the period 1850 to 1945. The first part analyzes the over-all consumption for the United States, and the second that by states. Population and consumption of persons over drinking age, which is placed at fifteen years, are compared.

Separate tables are given for consumption of distilled spirits (liquor) and wine and for total absolute alcohol contained in liquor, beer and wine. Chronic alcoholism is portrayed in a number of tables. The study was projected for the purpose of ascertaining the truth concerning the prevalent opinion that there has been an increase in drinking and a rise of alcoholism, particularly among women. The summary reveals that the per capita consumption of alcoholic beverages by persons of drinking age rose steadily during the course of World War II but remained below the levels of the pre-Prohibition years, and that the rise in consumption between 1940 and 1945, as shown by the tables, "was due to an increase of 35 per cent in the number of consumers, but individual consumption hardly increased if at all." Since 1850 the per capita consumption of distilled spirits has decreased by 53 per cent, whereas that of beer has increased by 862 per cent. The estimated number of chronic alcoholics was greatest in 1910. Between 1915 and 1920 the level dropped sharply, and the decrease was maintained during the Prohibition era. Between 1930 and 1945 the rate increased by nearly 28 per cent, but this rate was still 31 per cent below that in 1910.

The rate of female alcoholism was higher in 1910 than in 1945. The drop from 1915 to the Prohibition years was less in the female than in the male rate. Likewise, the rise of the female rate between the last Prohibition years and 1945 was only 12.6 per cent as compared with an increase of the male rate of alcoholism of 43.6 per cent. The entire rise in the female rate occurred during the war years. From 1940 to 1945 the female rate increased by 12.6 per cent, and the male rate by 22.6 per cent. Dr. Jellinek concludes that there is no basis for the contention that female inebriety is increasing faster than male inebriety. The rate of chronic alcoholism in cities of 100,000 and over is higher by 33.7 per cent than that in smaller cities and higher by 105 per cent than that in rural areas. The entire increase in the rate of chronic alcoholism since 1930 has been in urban areas, and the rate in the rural areas has decreased slightly.

There is a great variation in the rate by states owing largely to variation of the Dry sentiment. The statistics show that there was no shift in age at full-fledged alcoholism. This comprehensive survey is a valuable document and should be in all medical and reference libraries and in the libraries of persons interested in the subject.

Doctor, Don't Let Me Die! By S. S. Keiner, M.D. Collaborator, Dan Gorden. With an introduction by Henry E. Sigerist, M.D. 8°, cloth, 486 pp. Boston: Meador Publishing Company, 1947. $3.50.

The author, writing in a fictional form, has presented his views on the inadequacies of present-day medical practice and favors the passing of the Senate bill providing for a national health program. The book is essentially an autobiography.

Pharmakologie, als theoretische Grundlage einer rationellen Pharmakotherapie. By K. O. Moller, ord. Professor der Pharmakologie an der Universität Kopenhagen. Übersetzung und Bearbeitung nach der dritten dänischen Auflage von Dr. O. Walker. 4°, cloth, 744 pp., with 54 illustrations. Basel: Benno Schwabe and Company, 1947. 48 Swiss francs. Imported by Grune and Stratton, New York, N. Y.

This standard Danish work on clinical pharmacology is now available in a German-language translation. The subject is treated from the viewpoints of physiology and experimental pharmacology. The author has adopted a simple classification of ten divisions as follows: organic bacterial antiseptics; substances of predominant local action; chemotherapeutics, including the coal tars, sulfonamides and antibiotics; narcotics; alkaloids and other substances acting on the autonomic nervous system, cardiovascular drugs; substances predominantly acting on heat regulation and metabolism; vitamins, hormones and related body-regulating substances, including insulin and cortin; salts, acids, bases, light metals and metalloids; and heavy metals.

The material is well organized, and the text well written without redundancy. Under each drug there is given the chemical formula and chemistry, pathological actions and therapeutic indications; the official preparations of the German, Swiss and other pharmacopeias are also presented. Selected references of fundamental character are appended to the drugs when considered necessary. In addition, there is a forty-seven-page bibliography, arranged alphabetically by authors, following the text. This bibliography and the references are international in scope, embracing all languages and including a good representation of American and English writers. References as late as 1945 are cited. A comprehensive subject index concludes the volume. A valuable index of definitions is printed on page 724. The publishing is excellent in every way. The type is good, the margins wide, the paper soft, and the type page pleasing to the eye. Although the book is large, the weight is comparatively light for the size of the volume. It is a pleasure to handle such an excellent volume. This book should be in all medical schools, universities and large medical libraries, as well as in all collections pertaining to pharmacology and pharmacy. It is hoped that an English translation will be forthcoming.

Psychopathology: A survey of modern approaches. By J. Ernest Nicole, O.B.E., L.M.S.S.A., D.P.M.R.C.P. & S., medical superintendent, Winwick Mental Hospital. Fourth edition. 8°, cloth, 268 pp. Baltimore: Williams and Wilkins Company, 1946. $4.75.

In this new edition few changes have been made in the text, but the bibliography has been brought up to date so far as possible and comprises thirty-one pages made up entirely of monographs and books. The book is well printed with a good type on good paper with prewar margins. This short treatise should prove useful to persons interested in the subject.

A Manual of the Common Contagious Diseases. By Philip Moen Stimson, M.D., associate professor of clinical pediatrics, Cornell University Medical College, visiting physician, Willard Parker Hospital, director, Poliomyelitis Service, the Knickerbocker Hospital, medical director, The Floating Hospital of St. John's Guild, associate attending pediatrician, the New York Hospital, and consulting pediatrician, the Meadowbrook, Bergen Pines and Norwegian Lutheran hospitals. Fourth edition, thoroughly revised. 12°, cloth, 503 pp., with 67 illustrations and 8 plates, 6 in color. Philadelphia: Lea and Febiger, 1947. $4.00.

A large part of this new edition of a standard, authoritative manual has been rewritten, and much new material added to the text to bring it up to date, including a new chapter on the sulfonamides and the antibiotics. The chapter on poliomyelitis is essentially new. The bibliographies appended to each disease have also been brought up to date. A number of new illustrations have been added to the book. The printing is well done with a good type on good paper with wide margins. The manual should prove useful for quick reference purposes to physicians, nurses and health officers.

Occupational Diseases of the Skin. By Louis Schwartz, M.D., medical director, United States Public Health Service, chief, Dermatoses Section and associated clinical professor of dermatology and syphilology, New York University College of Medicine, and adjunct professor of dermatology and syphilology, Georgetown University School of Medicine; Louis Tulipan, M.D., clinical professor of dermatology and syphilology, New York University College of Medicine, consulting dermatologist, Manhattan General Hospital, and associate visiting dermatologist and syphilologist, Bellevue Hospital; and Samuel M. Peck, M.D., dermatologist, Mt. Sinai Hospital, New York City. Second edition, thoroughly revised. 8°, cloth, 964 pp., with 146 illustrations and 1 colored plate. Philadelphia: Lea and Febiger, 1947. $12.50.

This second edition of a standard reference book has been revised to bring it up to date. Material on new chemicals and new methods of manufacture, many developed during the war years, has been incorporated in the text. The volume is well published in every way and should be in all medical libraries, as well as in the libraries of dermatologists and physicians coming into contact with industrial dermatoses.

NOTICES

ANNOUNCEMENTS

Dr. Sydney J. Allman announces the opening of an office at 422 Beacon Street, Boston, for the practice of dermatology and syphilology.

Dr. William J. Clauser announces the opening of an office at 330 Dartmouth Street, Boston, for the practice of psychiatry.

Dr. A. H. Delman announces the opening of an office at 183 Babcock Street, Brookline, for the practice of otolaryngology.

Dr. Howard A. Hoffman announces the removal of his office to 60 Eighth Street, New Bedford, for practice limited to urology.

Dr. H. Sinclair Tait announces the opening of an office at 142 Main Street, Brockton, for the practice of psychiatry.

Dr. Sidney C. Wiggin announces the removal of his office to 270 Commonwealth Avenue, Boston.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, October 21, at 12 noon. Dr. John H. Cauley, health commissioner, City of Boston, will speak on "Problems of the Health Department."

This meeting will mark the beginning of the twenty-first year for the South End Medical Club. Physicians are cordially invited to attend.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The next meeting of the Middlesex South District Medical Society will be held at the Murphy General Hospital, Waltham, on October 22, at 12 noon, preceded by a business meeting at 11:30 a.m. Various papers will be presented by members of the hospital staff. Luncheon will be served at 1:00 p.m.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at 8 p.m. on Tuesday, October 28, at the Boston Medical Library, 8 Fenway, Boston, entitled "Lahey Clinic Night."

PROGRAM

The Present Status of the Peptic-Ulcer Problem. Dr. A. Allen Wilkinson.

Nonsurgical Proctologic Conditions. Dr. Neil W. Swinton.

Chronic Urethritis in Female Patients. Dr. Earl E. Ewert.

All physicians are invited to attend. A collation will be served.

CUSHING VETERANS ADMINISTRATION HOSPITAL

The following lectures will be presented at the Cushing Veterans Administration Hospital, Framingham, Massachusetts, at 4 p.m. on the dates indicated.

October 24. Dr. John P. Peters, professor of medicine, Yale University School of Medicine. "Some Problems of Edema."

October 30. Dr. Homer W. Smith, professor of physiology, New York University College of Medicine. "Hypertension and Urologic Disease."

October 31. Dr. Smith. "Renal Circulation."

STATE-WIDE HEALTH LEGISLATIVE CONFERENCE

The fourth Annual State-Wide Health Legislative Conference will be held in the Gardner Auditorium, State House, Boston, at 10 a.m. and 2 p.m., on Wednesday, October 29. All those interested in health legislation are invited to present their projects at that time and, if possible, to send word of them and any bill drawn to the Massachusetts Central Health Council, 1148 Little Building, Boston.

AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its annual convention at the Hotel Jefferson, St. Louis, Missouri, from December 15 to 17 inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy by registering without payment of fee. The program and the scientific and technical exhibits have been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as the results of investigation and research. Round-table conferences will be held on Monday afternoon, December 15. Advance copies of the program may be obtained by application to Dr. Charles H. Eyermann, chairman on arrangements, 634 North Grand Boulevard, St. Louis, Missouri.

(*Notices continued on page xvii*)